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APPLICATION OF SWEDISH QUALITY REGISTER DATA FOR USE IN HEALTH ECONOMIC ANALYSES OF CHRONIC CONDITIONS

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**Karolinska
Institutet**

Stockholm 2017

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Published by Karolinska Institutet.

Printed by E-Print AB 2017

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ISBN 978-91-7676-642-2

Application of Swedish quality register data for use in health economic analyses of chronic conditions

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*To Daniel, Siri, Frank,
the rest of my wonderful family and friends*

ABSTRACT

Sweden has many registers to monitor and follow-up healthcare, and combined with the unique personal identification numbers, this represents vast opportunities for register based research. Part of these data sources are the Swedish quality registers, which are set up to monitor the quality of care of specific diseases. Two of these registers that both have good national coverage over time and are used for research purposes are the Swedish Rheumatology Quality Register (SRQ) and the Swedish Stroke Register (Riksstroke). These are set up to monitor the quality of care of patients with rheumatoid arthritis (RA) and stroke, respectively, both diseases being associated with a chronic condition of functional disability. Data from the two quality registers have been used for scientific research in various fields, but to a lesser extent in health economic analyses.

Health economics addresses issues relating to the allocation of scarce resources to improve health. This includes resource allocation both within the economy to the healthcare system and within the healthcare system to different activities. Two common health economic approaches are economic evaluations of specific therapies and burden-of-illness studies, taking a broader analytical approach to a disease.

The overall aim of this thesis was to study the applicability of quality register data in health economic analyses of chronic conditions. The specific aims were:

- To assess the applicability of data from a quality register in economic evaluations of anti-TNF treatment for RA in clinical practice
- To assess the applicability of data from a quality register in burden-of-illness studies where health outcomes, resource use and costs of stroke are put in relation to each other

Data from the quality registers were used and linked to other relevant data sources to address the aims of this thesis. For the economic evaluations of treatments in RA, health economic models were constructed to enable the analyses. Statistical analyses were performed to allow for hospital comparisons of health outcomes and resource use for stroke, as well as estimating long-term transition probabilities for the health economic model in RA.

The papers concluded that:

- Anti-TNF therapies have on macro level been used cost-effectively as first-line biological treatment for RA in Swedish clinical practice. The cost-effectiveness results did not differ depending on the source of effectiveness data (clinical practice or RCT trial). However, the results were sensitive to the underlying progression rate of the comparator and assumptions made in the model.
- The impact of stroke on health outcomes, resources and costs were substantial. There were differences in performance between hospitals in these indicators that could not

be explained by differences in patient mix. The results further indicated that the costs differed by level of functional disability and age, up to two years post stroke.

Further, the papers of this thesis demonstrated the valuable contribution of quality register data in health economics in providing a valid base of data and opportunities to:

- Assess real life effectiveness of treatments in economic evaluations
- Retrieve data on health outcomes and patient characteristics, which are essential in:
 - Measuring health outcomes and relating them to levels of resource use
 - Enabling hospital comparisons of performance and performing case-mix adjustment of results
 - Enabling stratification of cost estimates by level of health outcome
 - Provide input parameters for future economic evaluations

In order to assess the full health economic aspects of chronic conditions, quality registers play an important role, but there is a necessity to combine the quality register data with other registers or other data sources, published literature and potentially also conduct modelling to account for the long-term effects. Nevertheless, any quality register that wants to ensure that the data can be used for health economic analyses and provide valid data for such analyses, should consider to:

- Ensure long-term follow-up of the patients (especially in chronic conditions)
- Collect data on:
 - Patient characteristics, including the clinical markers important for the patient's prognosis
 - Treatments received
 - Health outcomes that are common as measurements of treatment outcome (e.g. in RCTs), as well as estimation of quality of life or utilities
 - Resource use (quantifiable) outside the healthcare sector, e.g. informal care

The quality registers and other register data sources can be utilized to a greater extent in different assessments which share the aim of improving healthcare delivery and increasing its value – either by assessing level of health outcomes, processes and resources used; enabling comparisons between treatments or hospitals; or assessing determinants for different outcomes.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

- I. **Lekander I**, Borgstrom F, Svarvar P, Ljung T, Carli C, van Vollenhoven R.F. Cost effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. *Int J Technol Assess Health Care* 2010, 26(1) p.54-61
- II. **Lekander I**, Borgstrom F, Lysholm J, van Vollenhoven RF, Lindblad S, Geborek P, Kobelt G. The cost-effectiveness of TNF-inhibitors for the treatment of rheumatoid arthritis in Swedish clinical practice. *Eur J Health Econ.* 2012 Sep 19
- III. **Lekander I**, Kobelt G, Svarvar P, Ljung T, van Vollenhoven R.F, Borgström F. The comparison of trial data based and registry data based cost-effectiveness of infliximab treatment for rheumatoid arthritis in Sweden using a modeling approach. *Value in Health*, 2013, 16, p.251-258
- IV. **Lekander I**, Willers C, Ekstrand E, von Euler M, Fagervall-Yttling B, Henricson L, Kostulas K, Mikael Lilja M, Sunnerhagen K.S, Teichert J, Pessah-Rasmussen H. Hospital comparison of stroke care in Sweden: a register-based study. *Under revision in BMJ Open*
- V. **Lekander I**, Willers C, von Euler M, Lilja M, Sunnerhagen K.S, Pessah-Rasmussen H, Borgström F. Relationship between functional disability and costs one and two years post stroke. *PLoS One*, 2017, 12(4)

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADL	Activities of Daily Living
AF	Atrial Fibrillation
Anti-CCP	Anti-Cyclic Citrullinated Peptide
BOI	Burden-of-illness
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CMA	Cost-Minimization Analysis
CT	Computed Tomography
CUA	Cost-Utility Analysis
DALY	Disability-Adjusted Life-Years
DAS	Disease Activity Score
DES	Discrete Event Simulation
DMARD	Disease Modifying Antirheumatic Drugs
DTM	Dynamic Transition Model
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire Disability Index
HRQoL	Health-Related Quality of Life
ICD-10	10 th revision of the International Classification of Diseases and Related Health Problems
ICER	Incremental Cost-Effectiveness Ratio
ICH	Intracerebral Haemorrhage
IL	Interleukin
IS	Ischemic Stroke
KPB	Cost-Per-User
KPP	Cost-Per-Patient
LISA	Longitudinal integration database for health insurance and labour market studies
LtD	Dalarna County Council
LUL	Uppsala County Council

mRS	modified Rankin Scale
MTX	Methotrexate
NIHSS	National Institutes of Health Stroke Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PAS	Patient Administrative System
PREM	Patient Reported Experience Measure
PROM	Patient Reported Outcome Measure
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life-Years
RA	Rheumatoid Arthritis
RCT	Randomized Clinical Trial
RF	Rheumatoid Factor
RJH	Region Jämtland Härjedalen
RS	Region Skåne
RTB	Total population register
RÖ	Region Östergötland
SAH	Subarachnoid Haemorrhage
SF-36/6D	Short Form 36/6D
SG	Standard Gamble
SKL	The Swedish Federation of County Councils
SLL	Stockholm County Council
SoL	Care and social services for the elderly and for persons with impairments
SRQ	Swedish Rheumatology Quality Register
SSATG	South Swedish Arthritis Treatment Group
STM	State Transition Model
STURE	Stockholm TNF-alfa Follow-up Registry
TIA	Transient Ischemic Attack
TLV	The Dental and Pharmaceutical Benefits Agency
TNF	Tumour Necrosis Factor
TTO	Time Trade-Off

VAS	Visual Analogue Scale
VGR	Region Västra Götaland
WHO	World Health Organization
WTP	Willingness To Pay

1 INTRODUCTION

Sweden has many registers to monitor and follow-up healthcare. The personal identification numbers of individuals in Sweden are included in each of these registers, providing a unique opportunity to link data and perform evaluations on real life retrospective data over a range of aspects. Part of this flora of registers are held by the Swedish quality registers which are set up to follow diagnosis- and disease-specific health outcomes and healthcare processes in order to monitor the quality of healthcare (www.kvalitetsregister.se). There are more than 100 quality registers in Sweden, out of which approximately half are suitable for scientific research purposes. The quality registers can cover a wide range of variables, including healthcare resource use (such as length of stay or imaging procedures), clinical markers, patient reported outcome measures (PROM) and patient reported experience measures (PREM). Two of these registers that both have good national coverage over time and are used for research purposes are the Swedish Rheumatology Quality Register (SRQ) and the Swedish Stroke Register (Riksstroke), which are set up to monitor the quality of care of patients with rheumatoid arthritis (RA) and stroke, respectively.

Rheumatoid arthritis is a chronic auto-immune progressive disease that leads to restricted joint mobility, chronic pain, fatigue and functional disability. It usually has its onset in mid-life which means that patients can live with the disease and associated disability for many years (1). It is important to initiate effective treatment early in the course of the disease to limit the long-term effects on function, ability to perform daily activities and permanent damage of the joints.

Stroke is an acute disease caused by bleeding or ischemia in the brain. Early acute treatment is vital for survival and minimizing brain damage due to the stroke. Many patients have remaining disabilities after their stroke due to brain damage, with life-long consequences on, for example, the ability to perform daily activities (2).

Both RA and stroke are associated with chronic disability throughout the remaining life of the patient, although with different reasons for this disability. This has consequences on the health-related quality of life (HRQoL) of the individual patients (3), as well as a notable impact on society at large, in terms of both direct and indirect costs (primarily for RA) (4-9). Health economic analyses taking such effects into account can aid decision makers in ensuring cost-effective management of these patients in the long term. The SRQ and Riksstroke both contain information that are of importance in health economic analyses of RA and stroke, respectively, although they were not originally designed for health economic purposes. This thesis therefore assesses the applicability of quality register data in health economic analyses of these two chronic conditions.

1.1 RHEUMATOID ARTHRITIS

1.1.1 Pathophysiology

Rheumatoid Arthritis is a chronic auto-immune progressive disease characterized by inflammation. The immune system normally produces antibodies that attack bacteria or viruses to help fight infection. In RA, the immune system is instead attacking its own tissue, sending antibodies and/or autoreactive T-lymphocytes to the lining of the joints where they attack surrounding tissue. This causes the thin layer of cells (synovial membrane) covering the joints to become sore and inflamed, releasing inflammatory cytokines and enzymes that damage nearby bones, cartilage, tendons and ligaments. This causes the joints to lose its shape and alignment and eventually get completely destroyed. The cytokines damaging the joints are primarily Tumour Necrosis Factor (TNF) and Interleukin (IL-1 and IL-6), which also stimulates inflammation in patients RA (10).

In RA, the most relevant autoimmune antibodies are the Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). Laboratory tests can give an indication on the level of RF and anti-CCP present in the blood, which are considered predictors of the development of the disease. 75% of patients with RA show positive tests for RF and/or anti-CCP (11). B-cells are the source of RF and anti-CCP, and B-cells also contribute to T-cell activation through expression of stimulatory molecules (12). A simplified illustration over the pathophysiologic pathways in rheumatoid arthritis and their main clinical consequences is depicted in Figure 1.

High inflammatory activity and early joint erosion in the course of the disease is considered to be an indication for poor prognosis with fast disease progression (13).

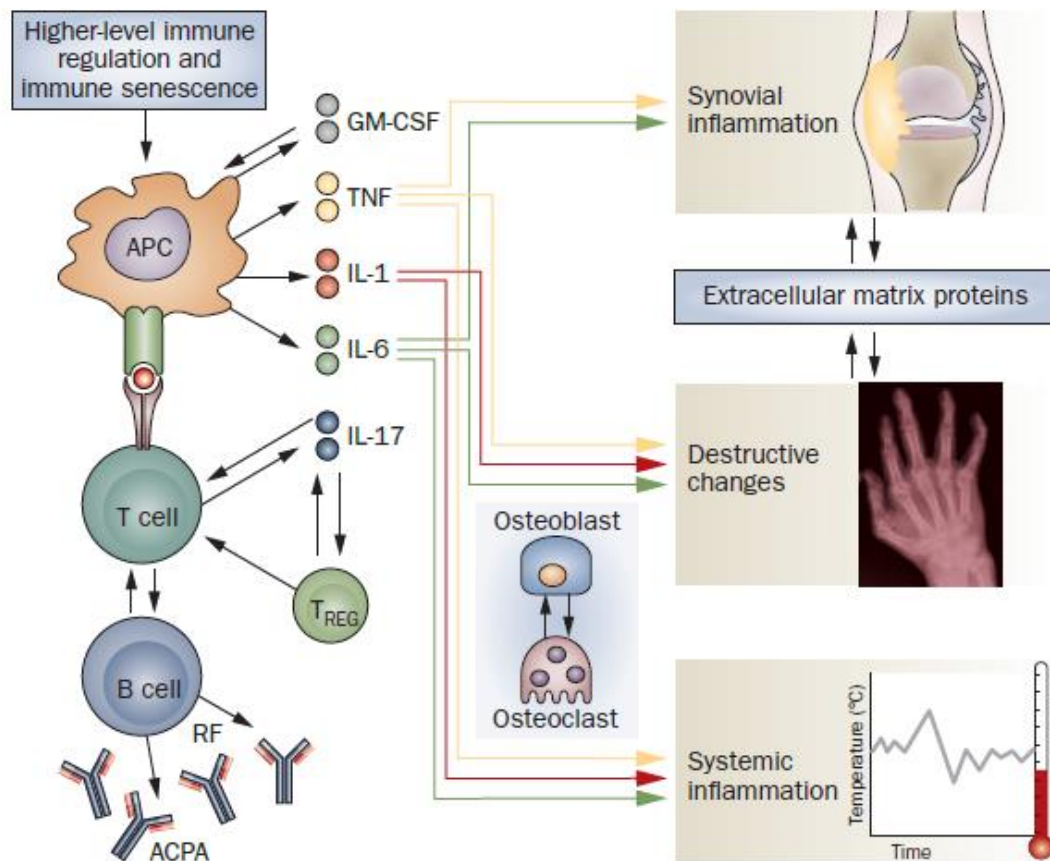


Figure 1. Simplified pathophysiologic pathways in rheumatoid arthritis and their main clinical consequences. Printed with permission from v Vollenhoven (10). Abbreviations: ACPA, anti-citrullinated protein/peptide antibodies; APC, antigen presenting cell; GM-CSF, granulocyte-macrophagecolony-stimulating factor; IL, interleukin; RF, rheumatoid factor; TNF, tumour necrosis factor; T_{REG}, regulatory T cell.

1.1.2 Epidemiology

The prevalence of rheumatoid arthritis is estimated to be 0.5–1.0 % worldwide (1), but the progressive nature of the disease and its onset in early or middle life means that patients can live for 30 or more years with the disease (1). The total number of patients with RA has been estimated to almost 2 million people in Europe and approximately 40,000 prevalent cases in Sweden (14). RA is more common among women than men, with a reported men-to-women ratio at 1:2 to 1:3 (14), but a higher proportion of men has been reported in the age group 45 to 64 (15).

An increased mortality rate has been noted for patients with RA, most often caused by cardiovascular disease (11). Other results of RA-related mortality are inconclusive; some studies have indicated that there was an increased mortality linked to functional status and disease activity whereas other studies were not able to demonstrate such an increase in mortality associated with RA during the first 10 years of follow-up (16-21).

The main effect of RA is the consequences on the patients' quality of life, as the disease can rapidly lead to restricted joint mobility (tender and swollen joints), chronic pain, fatigue, and functional disability. Approximately 20% of patients are unable to work during the years following the diagnosis (22) and one-third of the patients are unable to work within 10 years

of disease onset (4-6). The disease therefore has a considerable social and economic impact, and the costs to society associated with RA are substantial, both in terms of indirect and direct costs.

The cause of RA is unclear but more recent research has indicated that smoking can explain approximately 20% of the origin (11). Part of RA onset is explained by environmental factors and genetic predisposition (23), and potentially also by hormones as RA is more common in women than in men and often emerge while entering menopause (www.nhs.uk, www.1177.se).

1.1.3 Treatments

Early and correct diagnosis of RA is important to be able to initiate effective treatment and minimize the occurrence of joint destruction. Available treatments include both physiotherapy, which is important in order to maintain muscle strength and quality of life (11), and pharmaceutical treatments. As RA is a chronic disease, treatments are necessary during the remainder of the patient's life.

There are today several different types of pharmaceutical treatments available for patients with RA. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids are available to suppress inflammation (and relieve pain in the case of NSAIDs). Disease modifying antirheumatic drugs (DMARDs) are however more effective to suppress inflammation and thereby reduce the degradation of cartilage and bone. This in turn reduces the risk of permanent destruction of the joints. DMARDs can be non-biological or biological. Non-biological DMARDs act broadly on components active in RA, acting as anti-inflammatory or anti-metabolite agents (10). Non-biological DMARDs, specifically methotrexate (MTX) became more common in the 1990s, with intensified use earlier in the course of the disease (14), making a significant difference to the projected outcome for the patients. MTX is today commonly used as first-line therapy (11).

Biological DMARDs became available in 1999 with the ability to not only effectively control inflammation but prevent or slow the development of irreversible joint erosion (14).

Biological DMARDs include the anti-tumour necrosis factor agents (anti-TNFs) available since 1999, and other biological agents have become available in more recent years for the treatment of RA. The biological DMARDs block TNF, IL-1, IL-6 or B-cells producing RF and anti-CCP, dependent on the biological regimen (10) (see Figure 1). This development of different biological DMARDs provides an opportunity for patients to switch to alternative treatments if a treatment regimen has no or diminishing effect on disease progression (11). The treatments also have different modes of administration which may impact the choice of treatment regimen (for example is infliximab administered intravenous whereas the other anti-TNFs are administrated by infusion). Treatment results in newly diagnosed patients have improved continuously in recent years, following this development of biological DMARDs, where more patients now are in a state of low disease activity with limited functional

disability (11). More recent studies are also assessing different treatment schemes in early RA to minimize permanent damage (10) and ensure cost-effective use of treatment alternatives.

1.1.4 Treatment outcome

In randomized clinical trials (RCTs), there are two common treatment response criteria used; The American College of Rheumatology (ACR) response and the European League Against Rheumatism (EULAR) Disease Activity Score (DAS).

The ACR criterion is defining response as a percentage change from baseline in a core set of clinically relevant variables. 20% response (ACR20) is classified as a responder, but ACR50 and ACR70 are also often used as measures of response to capture the effect of biological DMARDs (24).

Classification of a responder on DAS is taking into account change in disease activity and current state of disease activity of the patients (24). In DAS28 (28 tender and swollen joint count) the scale is from 0-10, where a score below 3.2 indicates low disease activity and a score below 2.6 indicates a state of remission.

The Health Assessment Questionnaire Disability Index (HAQ) is another index used for assessment of functional status (10) on a scale of 0-3 where 0 is minimal functional disability. HAQ has been found to be strongly correlated to patients' quality of life and costs (25) and is often used in health economic analyses of RA.

1.2 STROKE

1.2.1 Pathophysiology

Stroke is defined by WHO as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” (26). However, there is an ongoing discussion about updating this definition to adapt to advances in science and technology, for example the 24-hour inclusion criterion is questioned as permanent injury can occur much sooner (27).

Nevertheless, stroke is a general term for conditions with common effects; decreased or completely blocked circulation in the brain's blood vessels which results in lack of function and, after a time, cell death in the affected parts of the brain. This in turn causes a risk of death or impairment of bodily function which may be substantial. A stroke can be caused by a blood clot (ischemia) or bleeding (haemorrhage), either intracerebral or subarachnoid (see Figure 2).

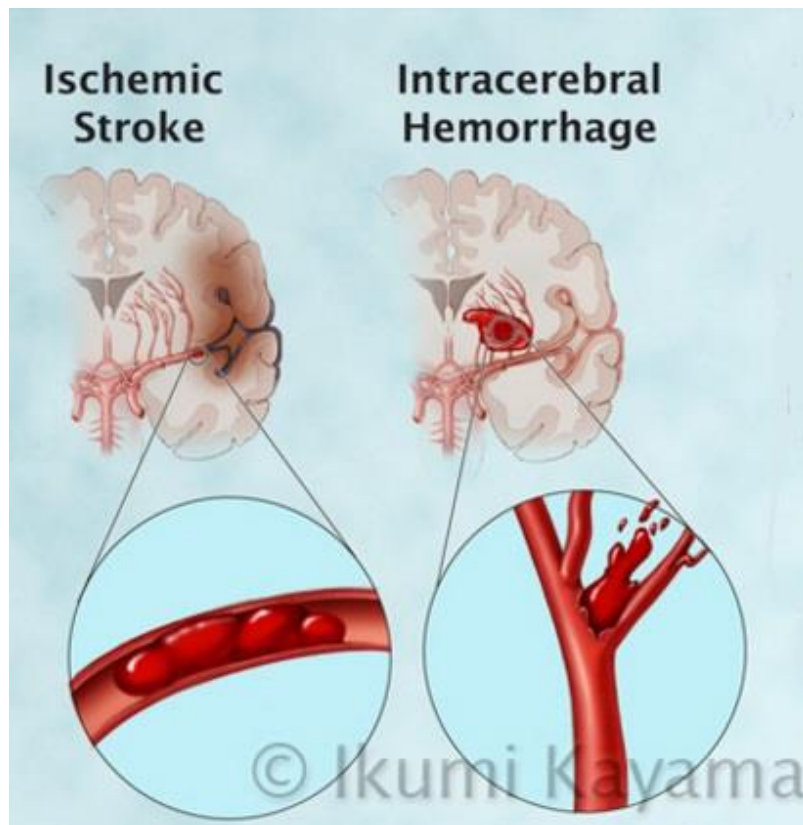


Figure 2. Illustration of ischemic stroke and intracerebral haemorrhage. Printed with permission from Ikumi Kayama (www.studiokayama.com)

An *ischemic stroke* (IS) is most commonly caused by a clot in the blood vessels in the brain or the neck, which leads to oxygen deficit in the affected area. If the clot has emerged in the occluded vessel it is called a thrombosis, mainly caused by atherosclerosis in the main vessel of the brain (28, 29). If the clot has emerged in a distant vessel (often a stenosis of the carotid artery) or in the heart (often due to atrial arrhythmias or faulty valves), it is referred to as emboli (29). Blood clots stuck in the brain's large vessels cause the most serious damage, especially when in *arteria cerebri media* (30).

The subtypes of IS have different aetiologies, risk factor profiles and different risks of mortality and new vascular events. The subtypes may be classified according to TOAST (31) in five categories;

- Cardioembolism, when the stroke is caused by an embolus arising in the heart, often associated with atrial fibrillation.
- Large artery atherosclerosis, caused by stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis.
- Small-vessel occlusion in the central brain, often labeled as lacunar infarcts. These patients often have a history of diabetes mellitus or hypertension.
- Other determined etiology, including patients with rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders.
- Undetermined etiology, when cause cannot be determined with any degree of confidence or two or more potential causes are identified.

Blood clots can be dissolved naturally within a short time, and thereby present a state of temporary stroke symptoms, called transient ischemic attack (TIA). A TIA is a warning of a high risk (10%) for actual stroke within two days, and TIA is therefore devoted considerable attention in the preventive work of stroke (30, 32).

A *haemorrhagic stroke* occurs when a blood vessel in the brain bursts (not because of trauma) with increased pressure and compression of surrounding tissue as a result (28). Brain haemorrhages can be classified based on where in the brain rupture occurs; inside the brain tissue (*intracerebral* [ICH], 10% of all strokes), respectively outside the brain tissue (*subarachnoid* [SAH], 5% of all strokes). SAH also yields a diffuse brain injury in contrast to the focal consequences of the other stroke types, and therefore has a different recovery trajectory.

1.2.2 Epidemiology

In Sweden, approximately 25,000 patients suffer an IS or ICH each year (2), out of which approximately 85% suffer from IS and 15% from ICH. Approximately 75% of these patients are having their first stroke, the rest are recurrent strokes. In addition to strokes, approximately 10,000 cases of TIA occur annually in Sweden. Over 80% of all IS or ICH cases affect individuals who are older than 65 years and are rather evenly distributed between men and women, although women on average are older at the time of their stroke (33). Stroke incidence has declined by approximately 1% annually since 2004 (34).

Risk factors for stroke are widely known and to a large extent potentially avoidable or treatable, except for age and sex (33, 35) (see Figure 3). The factors differ between the different subtypes of stroke, but are dominated by high blood pressure (hypertension) for both IS and ICH, and presence of cardiovascular source for emboli such as atrial fibrillation or narrowing of carotid arteries for IS (35, 36). Diabetes causes a moderate increase in stroke risk (35, 36). Smoking and obesity have also been shown to be associated with an increased risk of stroke (35, 37). Congenital heart defects and disorders of normal coagulation can for example also cause a stroke (28, 38). Several studies have indicated that significant portions of the lower mortality from stroke in recent decades probably can be attributed to better primary prevention therapy, primarily of high blood pressure (28, 36, 38).

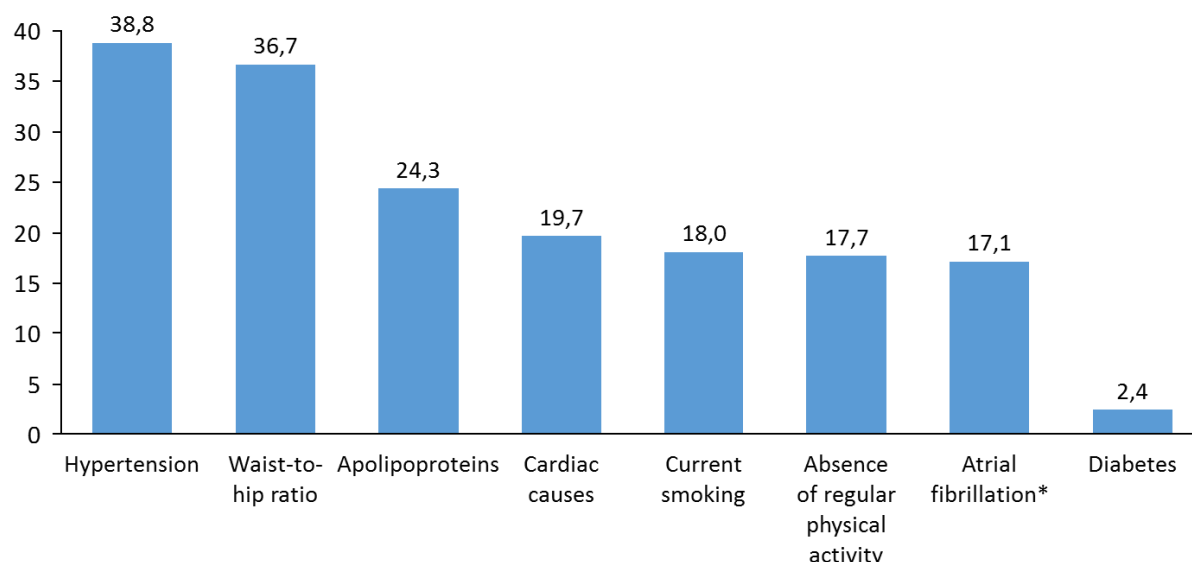


Figure 3. Patient attributable risks (PAR, %) of preventable risk factors for stroke for Western Europe, North America and Australia. Constructed from INTERSTROKE (35). Results adjusted for age, hypertension, smoking, waist-to-hip ratio, diabetes, physical activity, mAHEI, alcohol intake, psychosocial factors, apolipoproteins and cardiac causes were included in each model. *IS only

In Sweden, stroke is the most common cause of functional disability in adults and the third most common cause of death, after heart attack and cancer (2). The mortality rate is slightly higher for women than for men (2) and recent studies have shown that ICH account for half of all deaths from stroke, although IS is much more common (39). Many patients have remaining impairments after a stroke with life-long consequences on functioning (2) and healthcare costs (7-9). Hence, the effects of stroke on morbidity, mortality and costs both for the individual and for society are substantial (40, 41).

1.2.3 Treatments

Early acute treatment is vital for survival and minimizing brain damage after a stroke. Access to acute therapies has increased in recent years, which has had positive impact on the prognosis of the patients' health and has put increased emphasis on ensuring fast access to emergency care after stroke onset.

In principle, all incoming patients undergo a neuroradiological imaging (usually computed tomography, CT) to clarify whether the stroke is caused by a clot or a bleeding, as this determines the acute treatment options. In the case of IS, there are reperfusion treatments available as of recent years, namely thrombolysis (intravenous treatment that dissolves the clot) and thrombectomy (mechanical removal of the clot by catheter). Thrombolysis needs to be given within 4.5 hours from symptom onset and only when no contraindications exist. The sooner the treatment is performed, the better the prognosis for the patient. Contraindications to thrombolysis include for example recent surgery, ongoing treatment with anticoagulants and intracranial haemorrhages. Studies have shown that about 20% of stroke patients could be treated with thrombolysis, but that the level is lower for the majority of Swedish hospitals, although rising (34, 42).

Thrombectomy is usually performed when thrombolysis is considered inappropriate or when the desired effect from thrombolysis is not reached (34). The use of thrombectomy in Sweden is increasing, although still primarily performed at three Swedish university hospitals, implicating unequal access to this treatment within the country (42).

In malignant media infarction, a hemicraniectomy (surgical removal of part of the skull to relieve pressure off the brain) within 48 hours of onset can also be effective and has been shown to reduce deaths by 50% (32). This is however only relevant for a small part of the patient population.

If a patient has a haemorrhage, neurosurgical treatment, such as evacuation of the hematoma, may be a life-saving option. In cases where the patient has been treated with anticoagulants prior to the bleeding, coagulants are commonly used (43).

After acute management of the patients, the treatment focus is on rehabilitation and secondary prevention, often with life-long follow-up. Patients are cared for by a multidisciplinary team, which can include physicians, nurses, assistant nurses, occupational therapists, physiotherapists, social workers, speech therapists, dieticians and psychologists (with neuropsychological focus). The rehabilitation can for example include motor training, ADL-training (activities of daily living), language training and counselling regarding adaptation to acquired impairments in body function and activity.

Apart from inpatient care at a stroke unit or rehabilitation centre, the stroke patients may receive care through early supported discharge and continued rehabilitation in the home setting, as well as care at specialized outpatient clinics and primary care centres (important for secondary prevention). Many patients also receive home care service, home help or move into special housing provided by the municipalities (in the case for Sweden).

1.2.4 Treatment outcome

Outcomes in clinical trials and measurement of effect are often focused on mortality and functional disability after stroke. For degree of disability or ability to perform activities of daily living, the Barthel Index and modified Rankin Scale (mRS) have been used most extensively in clinical trials, both validated for stroke (44). The Barthel Index assesses the patients on a scale of 0-100 where scores above 60 is considered favourable, whereas mRS assesses the patients functional disability on the scale 0-6 where 0 is minimal functional disability and 6 is dead, and 0-2 is generally considered a favourable outcome (44).

These do not fully account for the quality of life of the patients. To assess the full consequences of stroke, instruments of assessing quality of life can be used as complements.

1.3 HEALTH ECONOMICS

Health economics has been defined as “the application of the theories, tools and concepts of economics as a discipline to the topics of health and healthcare. Since economics as a science is concerned with the allocation of scarce resources, health economics is concerned with

issues relating to the allocation of scarce resources to improve health. This includes both resource allocation within the economy to the healthcare system and within the healthcare system to different activities and individuals” (45).

A related theoretical framework is value-based healthcare, where value is defined as health outcomes achieved per money spent (46). Value-based healthcare has its ground in management theories and also includes aspects of healthcare organisation in order to maximize the value of healthcare.

Both frameworks have in common to put health outcomes in relation to the costs to ensure efficient use of limited resources. Both frameworks also put emphasis on the health outcomes relevant to the patients. Health economics, however, provides tools to analyse the healthcare system and its interventions, taking into account both health effects and costs which provides the main analytical framework of this thesis.

1.3.1 Health outcomes

Health is defined by WHO as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (Preamble to the constitution of the World Health Organization, Geneva, 1948). Depending on which aspect is most relevant for the analyses at hand, health outcomes can be assessed in several ways. Health outcomes could be categorized as either hard or soft endpoints:

Hard endpoints. These are health outcomes that can be measured objectively, for example mortality or incidence of cardiovascular disease. Clinical markers/endpoints can be considered as *intermediate or surrogate endpoints* for the health outcome of interest. For example, in diabetes, a well-maintained diabetes will decrease the risk of long-term complications such as cardiovascular events, although this effect is hard to assess at the time-point of treatment. Clinical markers such as HbA1C may therefore be used instead to assess the health effects of a treatment. RCTs often have clinical endpoints as a measure of efficacy. For health economic evaluations, a transformation from these surrogate endpoints to other health outcomes more relevant to the patients are often necessary as these are of greater interest for policy decisions (47).

Soft endpoints. These are often *patient reported outcome measures* (PROMs), commonly assessed by questionnaires that are completed by the patients. In health economics, Health-Related Quality of Life (HRQoL) is often of great interest, taking into account several different aspects of effects a disease has on the patient’s health. There are several validated quality of life instruments developed that are used for this purpose, both disease specific instruments and generic instruments such as the Short Form (SF)-36 (48). There are also other instruments and questionnaires assessing more specific health outcomes, such as experienced symptoms or ability to perform specific activities. *Patient reported experience measures* (PREM) are also measures reported by the patients (sometimes in the same questionnaire as PROMs), where questions refer to how the patients have experienced the

care that they have received. PREMs are, however, usually not classified as a health outcome, rather as an assessment of the care process.

In health economics, the term *utility* is often used when assessing the quality of life effects of a healthcare intervention. Utility in this setting is really a *preference* for a specific health state, expressed as a weight anchored between 0 (death or health state equivalent to death) and 1 (perfect health), and not a utility by its original theoretical definition. As stated by Drummond et al (49), preferences is by definition a broad term which includes both *values* (rational decisions under certainty) and *utilities* (rational decision under uncertainty). The measurement of preferences may be done through different methods, either scaling methods (e.g. rating scale or visual analogue scale [VAS]) or choice methods (e.g. time trade-off [TTO] or standard gamble [SG]). Only estimation by SG fulfils the original theoretical definition of utilities (decisions under uncertainty) as presented by von Neumann and Morgenstern (49), whereas the other methods results in a value. In this thesis, the term utility is, however, used in the commonly used broader meaning of the term.

There are validated generic questionnaires available (such as EQ-5D or SF-6D), where patients answer a few questions with regards to their current health state, and the results are thereafter converted into a preference weight or utility for that health state. The algorithms for conversion of the responses to a preference weight are most often based on published studies where a selection of responders from the general public have judged different health states by one of the choice methods (TTO or SG).

In economic evaluations, the preference weight (on the scale 0-1) is often multiplied with survival (life-years), resulting in a combined health outcome measure referred to as *quality-adjusted life-years* (QALYs). A QALY covers both mortality and quality of life effects of an intervention, and one QALY is interpreted as being equivalent to one year of life in perfect health. QALYs are useful when health outcomes in different diseases need to be put in relation to each other, e.g. in decisions on resource allocation within the healthcare system to different diagnostic areas.

1.3.2 Resources and costs

Attributing costs of healthcare to a treatment or a specific disease is not straight forward. All relevant resources need to be translated into measurable units, such as inpatient bed days, outpatient visits or hours of informal care. Thereafter a unit cost needs to be defined for each unit of resource and multiplied with the amount of resources.

In economic theory, the relevant cost is the opportunity cost, i.e. the benefit forgone from using resources for one purpose rather than in their best alternative use (45). This means that costs occur even in the absence of a financial flow, e.g. in the case of an informal carer. In practice, costing is often performed by using official price lists.

Which costs to include in a health economic analysis should be limited to the costs attributable to the treatment or the disease. It will also depend on chosen perspective, i.e. if

the analysis takes a payer perspective (only including costs incurred by the payer) or a societal perspective (including all costs irrespective of who incurs them) (45). Traditionally the societal perspective is employed in Sweden whereas some other countries apply a narrower perspective, such as to only consider costs affecting the healthcare sector (www.ispor.org).

Direct costs cover both medical costs such as hospitalizations, outpatient visits, procedures and services such as home care; as well as non-medical costs, such as transportations, home help, non-medical devices and informal care. Market prices are available for many of these resources but for some of them costing is less straight forward. For example, for informal care (care by e.g. relatives), the cost can be estimated based on the income lost due to the caregiver performing care (based on the caregivers' wage). However, time spent by the caregiver is not only conducted during working hours, rather the opportunity cost should also cover loss of leisure time, which is generally valued below earnings. Another method is to use market price of a close substitute (i.e. if the care service would have been bought instead), referred to as the replacement cost method.

Indirect costs refers to productivity losses incurred when patients are on sick leave, have reduced productivity at work, end up in early retirement or die prematurely related to the specific disease (45). Indirect costs are commonly priced with the human capital approach, which values the lost production with gross earnings (50). Critiques against this method argue that sooner or later the lost capacity will be replaced, and hence the productivity loss will diminish. A method to account for this is referred to as the friction cost method (51). Since indirect costs refer to lost productivity, it only incurs in the years when the patient is part of the workforce. In diseases with a chronic disabling condition such as RA and stroke, indirect costs may be substantial if onset is while the patients are still participating in the workforce.

Intangible costs are costs related to loss in quality of life or suffering for the patient due to a disease or a treatment. These costs are, however, difficult to estimate and are usually included in the health outcomes dimension in the case of a health economic evaluation.

Costs in added life-years appears when an intervention prolongs the life of patients as the increased survival also can be associated with a cost to society, that is not directly related to the treatment or disease evaluated. This cost represents the difference in consumption and production over the gained number of life years. Individuals over retirement age most often consume more resources than they produce, while younger produce more than they consume (52, 53).

In cases where treatment prolongs life but does not keep patients in the workforce, the inclusion of indirect costs and cost in added life years only adds to the cost of keeping patients alive. This may be problematic from an ethical point of view as it can discriminate patient groups far from the workforce if the analysis is used for decision making. More recent recommendations by the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden

therefore suggest that in these circumstances, the indirect costs and costs in added life years may be omitted from the analysis (www.tlv.se).

1.3.3 Health economic analyses

Health economic analyses are studies which consider both health aspects and costs (or resources). Broadly, health economic analyses can either be an economic evaluation of a specific intervention or a burden-of-illness study which attempts to assess the total burden of a disease on a society.

Economic evaluations

An economic evaluation has been defined as “the comparative analysis of alternative course of action in terms of both their costs and consequences” (54). Economic evaluations give information on a treatment alternative compared to (at least) one other alternative, which may serve as basis for decisions of resource allocation within the healthcare system.

The term *cost-effectiveness analysis* is often used to describe the economic evaluation at hand. However, there are different types of economic evaluations which are dependent on how the health outcome (effect) is assessed:

- Cost-minimization analysis (CMA): when the treatment options have equal effects and only costs are compared
- Cost-effectiveness analysis (CEA): when outcome is one-dimensional, e.g. life-years gained, events avoided
- Cost-utility analysis (CUA): when outcome is two-dimensional, e.g. life-time gained and quality of life combined into QALYs
- Cost-benefit analysis (CBA): when outcome is measured in monetary terms

The most common type economic evaluation is the CEA or CUA. The results of these analyses are presented as an incremental cost-effectiveness ratio (ICER), which is defined as the incremental cost (C) divided by the incremental effect (E) of one intervention (A) compared to best available alternative (B):

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_A - C_B}{E_A - E_B}$$

The ICER is interpreted as the incremental cost to gain an extra unit of health outcome, for example the cost per life-year gained. Whether a result is to be considered cost-effective or not will depend on the willingness to pay (WTP) for an additional unit of health outcome. In Sweden for example, cost-effectiveness analyses are performed for new pharmaceuticals and submitted to TLV for reimbursement approval. One of the criteria for the decision is cost-effectiveness, and TLV will in their decision compare the ICER and the uncertainty around this estimate to the WTP. The WTP is not at a fixed level, it rather tend to be higher for more severe diseases such as cancer, but has historically been around €65,000/QALY gained (55).

Economic evaluations often need to combine data from several sources, e.g. clinical trials, registers, observational data and other published data on resources, costs and outcomes. Additionally, data may only be available for a short follow-up (e.g. in the case of RCTs) and there may be a need for extrapolation over time. *Models*, defined as “mathematical frameworks that facilitate estimation of the consequences of healthcare decisions” (56), are useful in economic evaluations, enabling all relevant costs and consequences to be taken into account. A model is a simplification of reality where the course of the disease and the main effects of the treatment are mirrored. The choice of modelling technique or software does not matter to the results as long as all relevant costs and effects are included and the model is structured in a correct manner. The choice of model should be based on what is most appropriate for the disease and course of action of the treatment, as well as data availability.

For example, a decision tree model (see Figure 4) is a simple form of model, suitable for analyses with a short-term horizon or when the possible number of outcomes is limited. In this example, there is one treatment arm and one comparator arm, where the patient can either get cured or die. For each choice, the treatment (treatment arm) is compared to no treatment (comparator arm), all costs and effects (proportion cured) are summarized at the end of the tree and compared to each other.

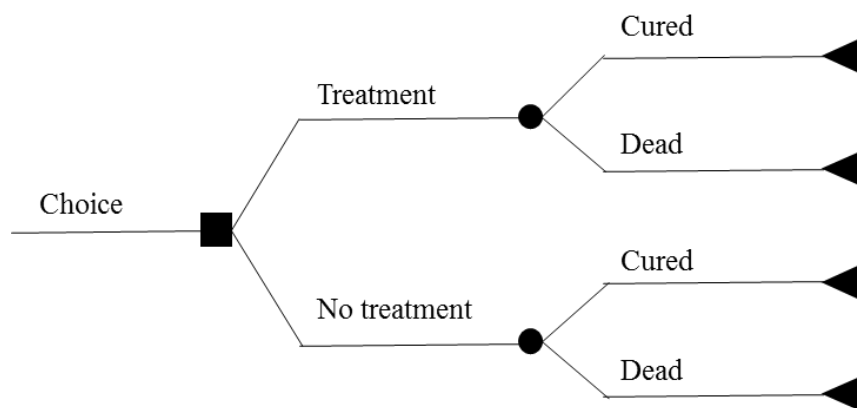


Figure 4. Decision tree model

In economic evaluations, however, more advanced models are most often necessary and different models holds different attributes which makes them more or less suitable for the analysis at hand. A summary of the main model types, their attributes and where the models are most suitable are listed in Table 1.

Table 1. Summary of main model types

Model type	Main sub types	Attributes	Suitable for
State-transition models (STM) (57)	<ol style="list-style-type: none"> 1. Cohort model or “Markov model” 2. Individual based model or “first-order Monte Carlo” or “micorsimulation” 	<p>States – a condition an individual can be in. All states are mutually exclusive and collectively exhaustive</p> <p>Transitions – how the cohort/patients move among states</p> <p>Transition probabilities – how likely these moves are</p> <p>Cycle – time interval when transitions are possible</p>	Evaluation of risk factor interventions, screening, diagnostic procedures, treatment strategies and disease management programs
Discrete event simulation (DES) (58)	<ol style="list-style-type: none"> 1. Non-constrained resource model 2. Constrained resource model 	<p>Entities – are the objects, in healthcare mainly patients</p> <p>Attributes – features specific to each entity to carry information (e.g. risk factors, QoL), can be modified over time</p> <p>Events – things that can happen to the entity. These are mutually exclusive (discrete)</p> <p>Resource - an object that provides service to an entity, can be “occupied” which creates queues.</p> <p>Time - Model jumps from the time of one event to the time of the next</p>	<p>In cases where patients are subject to multiple or competing risks and time dependencies are important.</p> <p>Suitable when resources are constrained or limited</p>
Dynamic transmission models (DTM) (59)	<p>Any sub-type possible, e.g.:</p> <ul style="list-style-type: none"> • Deterministic or stochastic • Individual or cohort based 	Dynamic function of risk, taking into account number of infectious individuals in the population at a given point in time	<p>Suitable when evaluating an intervention against an infectious disease that:</p> <ul style="list-style-type: none"> • impacts a pathogens ecology or • impacts disease transmission in target population

The choice of subtype of a model may come down to convenience. For example, a cohort simulation STM should be chosen if the decision problem can be represented with manageable number of health states that can incorporate all characteristics that are relevant to the decision problem. If instead the representation ends up with an unmanageable number of states, then an individual level STM is preferred, although such model in general is more complex and less transparent (57).

A STM is often illustrated in a state transition diagram where the arrows indicate all possible transitions from one state to another (or possibility of remaining in current state) (Figure 5). Dead is always an absorbing state where the patients remain throughout the simulation. Each health state is associated with a cost and a health effect and at the end of the simulation (e.g. a pre-defined timeframe of 20 years), all costs and effects for the comparing alternatives are summarized.

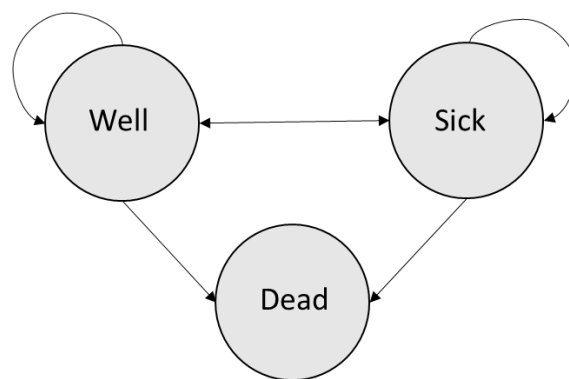


Figure 5. STM model state transition diagram

Burden-of-illness

Burden-of-illness analyses (or commonly referred to as cost-of-illness when expressed in monetary values) are not designed to assess specific interventions, rather estimate the burden a specific disease has on society. As these studies do not assess the effect on health outcomes by an intervention, it is not an economic evaluation and cannot demonstrate where resources should be allocated to improve health outcomes. These studies can, however, inform policy makers on the burden or severity of a disease, which can be useful in planning and making budget decisions and decisions on resource allocation within the economy, as well as serve as input data in specific economic evaluations (45). Burden-of-illness methodology covers direct, indirect and intangible costs related to a disease. However, the latter is commonly not translated into monetary values, but rather expressed as quality of life, QALYs or Disability-Adjusted Life-Years (DALYs) (60). Direct and indirect costs can also be expressed either as amount of resources utilized or in monetary terms.

In a prevalence based approach, all cost items for a disease in a given geographical area is collected for a specific time-period, covering all patients with the specific disease. In an incidence based approach, on the other hand, estimates cover the time from diagnosis to cure (or death in the case of chronic diseases) (45). Results from these studies are often presented

on a total population basis, but can also be presented on a per-patient basis or separated for specific sub-groups of patients.

Further, method chosen to do a burden-of-illness study can be top-down or bottom-up. In a top-down study e.g. a register may be used to estimate the costs for a given sample of patients. Using a bottom-up method, all costs would instead be collected directly from the patients, either from questionnaires retrospectively or following the patients prospectively for a given time. The top-down method may underestimate the burden when not all information is available in public records but it is a method which is relatively time efficient and allows for inclusion of large datasets. A bottom-up method on the other hand is more costly and time-consuming and puts higher emphasis on ensuring that the patient sample is unbiased and representative to be able to draw general conclusions, although allowing for a more coherent coverage of resources or health outcomes (45).

1.4 PREVIOUS STUDIES BASED ON SWEDISH QUALITY REGISTER DATA

Quality registers in Sweden are used for many scientific purposes and many papers have been published based on the data. However, their use in health economic analyses has been more limited, although usage for these purposes has increased in later years. A selection of health economic analyses based on Swedish quality register data covering patients with RA or stroke are listed in Table 2. These either uses methodology of economic evaluations or burden-of-illness analyses, where the latter either assessed indirect costs, direct costs or both (expressed either in resources/productivity loss or costs). Furthermore, Swedish quality register data has also been used in health economic analyses of diabetes (61-64), MS (65, 66) and cancer (67-71), among other diseases, however omitted from this summary.

Table 2 Selected health economic analyses based on Swedish quality register data for patients with RA or stroke

	Author	Title	Year	Quality register	Health economic aspect
RA	Eriksson et al (72)	Cost-effectiveness of infliximab versus conventional combination treatment in methotrexate-refractory early rheumatoid arthritis: 2-year results of the register-enriched randomised controlled SWEFOT trial.	2015	SRQ	Economic evaluation: CUA
	Kobelt (73)	Treating to target with etanercept in rheumatoid arthritis: cost-effectiveness of dose reductions when remission is achieved	2014	SRQ	Economic evaluation: CUA
	Lindgren et al (74)	Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden	2009	SRQ (SSATG)	Economic evaluation: CUA
	Neovius et al (75)	Sick leave and disability pension before and after initiation of antirheumatic therapies in clinical practice.	2011	SRQ	BOI: Indirect cost
	Neovius et al (22)	How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop	2011	SRQ	BOI: Indirect cost
	Augustsson et al (76)	Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry)	2010	SRQ (STURE)	BOI: Workforce participation
	Kobelt et al (77)	Costs and outcomes for patients with rheumatoid arthritis treated with biological drugs in Sweden: a model based on registry data.	2009	SRQ (SSATG)	BOI: Direct costs
Stroke	Steen Carlsson et al (78)	Long-term cost-effectiveness of thrombectomy for acute ischaemic stroke in real life: An analysis based on data from the Swedish Stroke Register (Riksstroke)	2017	Riksstroke	Economic evaluation: CUA
	Sunnerhagen et al (79)	WebRehab: a Swedish database for quality control in rehabilitation	2014	WebRehab	BOI: Direct costs
	Gathnekar et al (80)	Costs for stroke in Sweden 2009 and developments since 1997	2014	Riksstroke	BOI: Direct & indirect costs
	Persson et al (81)	Economic burden of stroke in a large county in Sweden	2012	Riksstroke	BOI: Direct & indirect costs
	Gathnekar et al (82)	The effect of Atrial Fibrillation on Stroke-Related Inpatient Costs in Sweden	2008	Riksstroke	BOI: Direct costs
	Lindgren et al (83)	Utility loss and indirect costs after stroke in Sweden	2008	Riksstroke	BOI: Indirect costs
	Gathnekar et al (7)	Cost of stroke in Sweden: An incidence estimate	2004	Riksstroke	BOI: Direct & indirect costs

BOI = Buren-of-illness

1.4.1 Economic evaluations

Three articles investigated the cost-utility of different treatment alternatives for RA, based in part on data from the SRQ. The first article, by Lindgren et al, modelled the cost-effectiveness of Rituximab as second-line biological treatment (74), utilizing data from SRQ (different parts of the register) for identifying the study cohort, retrieving patient characteristics (e.g. gender, age, years since diagnosis, disease severity) as well as the estimated effectiveness of the treatments modelled based on functional capacity (HAQ) and disease activity (DAS28) scores. The second study, by Kobelt et al (73), estimated cost-effectiveness of dose reduction of anti-TNF treatment when remission is achieved (three different strategies), where “standard therapy” after failure of the intervention therapy being discontinued was taken from SRQ, i.e. the transition probabilities after treatment failure for up to 10 years. The third study, by Eriksson et al (72), evaluated the cost-effectiveness of infliximab use compared to conventional therapy in patients with MTX-refractory early rheumatoid arthritis, based on the SWEFOT clinical trial, using data from SRQ for assessing drug use for costing purposes (not effectiveness).

The study evaluating Rituximab found this therapy to be a cost-saving alternative to anti-TNF treatment after failure of the first anti-TNF treatment (74). In the study on dose reduction, the strategy of dose reduction of anti-TNF therapy while in remission was found most advantageous from a health economic perspective (73). The study in early MTX-refractory RA-patients, infliximab therapy was not found to be cost-effective over a 21-month period (72). Other studies evaluating biological treatments for RA in clinical practice in other countries have reached similar conclusions as in these studies (84-86).

One recent article with a cost-effectiveness focus on stroke treatment was identified, evaluating the cost-effectiveness of thrombectomy after thrombolysis (78). This study by Steen Carlsson et al (78) used data from Riksstroke on the need for healthcare and social services for patients with severe ischemic stroke, stratified by age and mRS-status. Effectiveness data were retrieved from clinical trials. The results indicated that thrombectomy was cost-saving when accounting for the costs saved in the social service sector. Additionally, in an article by Ghatnekar, a cost-effectiveness assessment of admission to stroke unit was performed as part of a study, indicating reasonable levels of cost per life years gained (<€20,000). This assessment was based on data from Riksstroke to identify the cohort, patient characteristics, resource use, living conditions, functional ability (ADL) and admission to stroke units.

Cost-effectiveness analyses have also been conducted on thrombolysis based on clinical trial data, where data on outcome and costs has been retrieved from patient registers in a UK setting (87). The number of such analyses is today scarce, however expected to increase as these therapies becomes more common in clinical practice and longitudinal data becomes available for example in Riksstroke.

1.4.2 Burden-of-illness analyses

Four studies have used data from SRQ for estimating different cost-components of RA. Two articles by Neovius et al (22, 75) were tightly linked, one estimating sick leave and disability pension in patients diagnosed with early RA (22) and the other investigating sick leave and disability pension among patients with RA in relation to initiation of biological and non-biological therapies (75). The outcome of sick leave and disability pensions were retrieved from Swedish Social Insurance Agency (Försäkringskassan) in both studies and SRQ was used to identify the patient cohort as well as in retrieving patient characteristics. Both studies indicated that productivity losses increased the years before diagnosis and before initiation of antirheumatic therapies (22, 75). Treatment initiation halted this development of increase in productivity losses although it did not reverse it. In a study by Augustsson et al (76), these findings were further confirmed as it showed that initiation of biological therapy increased workforce participation. This study used data from the SRQ for cohort identification and patient characteristics, but also used the information on workforce participation as collected within the Stockholm part of SRQ (STURE database). However, indirect costs as a consequence of RA were not estimated. Kobelt et al (77) investigated costs and outcomes for RA patients treated with biological treatment. The analysis was based on data from SRQ for identifying the patient cohort and patient characteristics, but also outcomes on HAQ and linking this to cost estimates. Resource consumption was based on a survey. This study estimated both direct and indirect costs of RA as well as determinants of resources use, which were found to be sensitive to functional capacity at treatment initiation (HAQ), disease progression, age and disease duration.

Further, in a study by Kalkan et al (88), a shift in cost composition over time for patients with RA in Sweden was indicated, where the cost of biological DMARDs has increased whereas costs for inpatient care and indirect costs have decreased. This was a Swedish register based study, although no data from a quality register was used in this assessment.

The cost-estimates from the two studies presented in Table 3 indicated similar levels for indirect costs in a Swedish setting, when taking different time horizons, cohorts and different methods for estimations (register versus survey) into account.

Table 3 Cost estimates of RA

Study	Details	Direct costs	Biological treatment	Indirect cost	Year of prices
Neovius et al (22)	1 year cost, excess productivity loss			92,000 SEK	2007
Kobelt et al (77)	Start HAQ 1.33, 5 year horizon	200,000 SEK (40,000 SEK/year)	500,000 SEK (100,000 SEK/year)	600,000 SEK (120,000 SEK/year)	2008

Riksstroke has been used for several assessments of cost-components of stroke. Three articles by Ghatnekar et al (7, 80, 82) and one by Lindgren et al (83) have used Riksstroke for identifying the cohort and determining patient characteristics. In a cost assessment by Ghatnekar (80) comparing the cost of stroke in Sweden 2009 to 1997, the cost estimates were based on resource use as measured in Riksstroke at admission, after three months and after twelve months. The study had a societal perspective. In another study by Ghatnekar (7), data for resource use was instead retrieved from the national patient register, although the cohort, patient characteristics and need for assistance were still based on Riksstroke. As the second study had access to the total amount of healthcare resources used by the patient (inpatient and outpatient visits) whereas the first only had what was registered in the acute forms from Riksstroke, the direct costs were estimated to be higher in the second study whereas the estimates for indirect costs reached similar levels in both studies.

The effects of determinants of cost estimates were investigated in the third study by Ghatnekar et al (82), concluding that strokes related to atrial fibrillation (AF) were associated with higher costs than non-AF related strokes. These findings were based on patient characteristics and cohort selection from Riksstroke whereas resource use was estimated based on the national patient register. The study by Lindgren et al (83) used a survey to estimate the productivity losses due to stroke, based on a cohort from Riksstroke. In Persson et al (81), the economic burden of stroke in one Swedish region was estimated, using macro data from Riksstroke on municipality care and informal care, presenting the excess costs both separately for the first three years and as expected life-time costs.

In all, the estimates of indirect costs in the different studies were in line with each other, although the level of costs was set at different years. For direct costs the comparison is not as straight forward as the different articles have different time horizons, methods for estimation and inclusion of cost-items (see Table 4). Two additional Swedish studies (89, 90) based on register data (although not containing data from a quality register) found the costs to be in line with the findings of Persson et al (81).

In an article by Sunnerhagen et al (79), the WebRehab quality register was used, assessing length of stay for patients at rehabilitation clinics, among those patients with stroke. Out of those admitted, stroke patients had on average 37 days in rehabilitation clinic. It should be noted that this is only a subset of the total stroke population.

Table 4 Cost estimates for stroke

Study	Cost horizon	Direct Costs	Indirect Costs	Year for price
Ghatnekar et al 2014 (80)	Life-time	€54,000	€14,500	2009
Ghatnekar et al 2004 (7)	Life-time	€60,800	€ 14,800	2000
Ghatnekar et al 2008 (82)	3-year	€9,000		2001
Persson et al 2012 (81)	First year	€17,000 ²	€4,000 ²	2008
Hallberg et al 2016 ¹ (89)	First year	€10,000		2012
Banefeldt et al 2016 ¹ (90)	First year		€6,800	2012
Lindgren et al 2007 (83)	First year (<65)		€13,200	2006

1. Register data but not from a quality register, only county council resources, Banefeldt et al only for working age;

2. Approximation from graph

1.4.3 Knowledge gaps

Most studies using quality registers for health economic purposes in Sweden have used them primarily to identify the patient cohort and retrieve information on patient characteristics. For both RA and stroke, there is a potential to further utilize the data available within the quality registers for health economic purposes. Specifically, there is an opportunity to increase the knowledge in:

- Estimating the cost-effectiveness in clinical practice of different treatment alternatives and how these compare to clinical trials.
- Estimating health outcomes and relating them to resources and costs

2 AIMS OF THESIS

The overall aim of this thesis was to study the applicability of data from quality registers in health economic analyses of chronic conditions. The specific aims were:

- To assess the applicability of data from a quality register in economic evaluations of anti-TNF treatment in clinical practice for rheumatoid arthritis
- To assess the applicability of data from a quality register in burden-of-illness analyses where health outcomes, resource use and costs of stroke are put in relation to each other

All papers of this thesis were based on quality register data to assess different health economic aspects. The different papers have the following specific aims, all for the Swedish setting:

- I. To estimate the cost-effectiveness of infliximab use in patients with rheumatoid arthritis in clinical practice.
- II. To estimate the cost-effectiveness of anti-TNF therapy for the treatment of rheumatoid arthritis in clinical practice, both as a first and second biological treatment, with or without the combination of conventional DMARDs.
- III. To evaluate the precision of the predictive cost-effectiveness assessment based on a phase 3 clinical trial with infliximab for the treatment of rheumatoid arthritis in clinical practice.
- IV. To estimate the level of health outcomes and resource use on hospital level during the first year after stroke, and to analyze any potential differences between hospitals after adjusting for patient characteristics (case-mix adjustment).
- V. To estimate the costs of stroke care by level of disability and stroke type.

3 MATERIALS AND METHODS

3.1 RHEUMATOID ARTHRITIS COHORT

The cohort of patients with rheumatoid arthritis was taken from the SRQ for papers I-III. In paper III, an additional cohort of patients was identified from the phase III ATTRACT trial for infliximab therapy.

3.1.1 Swedish Rheumatology Quality Register (SRQ)

The SRQ collects data on patient reported health status, clinical and laboratory data as well as information on treatments received. Biological treatments have been monitored on a national level in SRQ since their introduction in 1999. SRQ is a network of several registers, together providing national coverage of approximately 80% of all RA patients (www.srq.nu) (91).

Patient level data was retrieved from three data sources that are part of the SRQ. Data from the Stockholm TNF-alfa Follow-up Registry (STURE) was used for papers I-III. In addition, paper II included data from South Swedish Arthritis Treatment Group register (SSATG) and the Falun section of SRQ, providing a wider geographical spread across the country in the patient cohort. Because data from the first introduction of anti-TNFs on the Swedish market was available, it was possible to classify patients according to their first- or second-line biological DMARDs (anti-TNF therapy). The SRQ includes only a limited number of patients without biological DMARDs, and a comparison to a population without biological DMARD was hence not possible based on quality register data.

The full dataset for papers I-III consisted of patients initiating treatment with any anti-TNF treatment between 1998 and 2008, constituting approximately 90 % of all RA patients treated with biologics in the regions covered for the specific time-period.

3.1.2 ATTRACT trial

The ATTRACT trial was the pivotal RCT where patients were randomized to infliximab plus MTX or to placebo plus MTX, receiving treatment every 8 weeks for 1 year. The double-blinded period was followed by an open extension (92, 93).

Aggregated data from the ATTRACT trial was used in paper III.

3.1.3 Study populations and variables

The study population in paper I consisted of 637 patients receiving infliximab therapy as their first-line biological therapy, from the STURE part of the SRQ.

The study population in paper II consisted of 2,558 patients receiving any anti-TNF therapy as their first-line biological treatment, from the STURE, SSATG and Falun part of the SRQ.

In paper III, three cohorts were identified, where the first two were elicited from the study population in paper I:

1. All patients receiving infliximab therapy as first-line treatment (637 patients) from the STURE part of SRQ.
2. All patients receiving infliximab therapy as first-line treatment from the STURE dataset, and who met the RCT inclusion criteria (306 patients, 48% of the STURE dataset).
3. Patients in the ATTRACT trial randomized to infliximab therapy (287 patients) or placebo (58 patients).

Data on disease progression over states of HAQ and DAS28 during treatment, treatment regimen, line of biological treatment as well as discontinuation rates from the SRQ dataset were used for papers I, II and III.

Data on patient characteristics, effectiveness (HAQ and DAS28 transitions) and treatment discontinuation was retrieved from the ATTRACT trial on aggregated level for paper III.

3.2 STROKE COHORT

The patient cohort for papers IV and V was retrieved from the quality register Riksstroke and the patient administrative systems of seven Swedish regions. This was complemented with data from several other Swedish national registers.

3.2.1 Swedish Stroke Register (Riksstroke)

The Swedish Stroke Register (Riksstroke) is the national quality register for stroke care, monitoring patients with IS, ICH or unspecified stroke as well as patients with TIA. Patients with SAH are not included in the register. The register entails, among other, information on acute treatment, first admission to hospital, secondary prevention, PROMs and PREMs. The registry collects data at admission for acute stroke and after three and twelve months, respectively. All hospitals admitting patients with acute stroke collect and reports data to Riksstroke. The national coverage of the acute form has been estimated to 96% after validation when compared to the national patient register (34). The coverage for the three and twelve months' forms are estimated to be 88% and 81%, respectively, out of those with an acute form in Riksstroke and who are still alive at time of follow-up (www.riksstroke.se). The form at admission and three months are completed by the treating clinic (including patient interview or questionnaire for the PROM and PREM measurements) whereas the form at twelve months is sent out to the patients from Riksstrokes central administration.

Patient level data was retrieved from Riksstroke, consisting of all patients with an acute stroke (IS or ICH) registered in Riksstroke between 2007 and 2012 in any of the following Swedish regions: Jämtland Härjedalen (RJH), Östergötland (RÖ), Dalarna (LtD), Uppsala (LUL), Skåne (RS), Stockholm (SLL), and Västra Götaland (VGR). The included regions were those participating in the Sveus research program (www.sveus.se). This selection covers approximately 60% of all strokes annually in Sweden.

Data on patient characteristics and health outcomes (PROMs) for this study population was used in papers IV and V.

Functional ability was assessed through mRS, and good functioning was defined as mRS 0-2. Riksstroke does not collect mRS but contain variables that enables an estimation of mRS at three and twelve months post stroke, based on algorithms validated by Eriksson et al (94).

3.2.2 Patient administrative systems (PAS)

Each region in Sweden has a patient administrative system which collects data on all healthcare contacts a patient has, including date of visit or admission, diagnosis and procedure codes (ICD-10 and KVÅ, respectively) as well as information about the hospital. Data from seven Swedish regions (RJH, RÖ, LtD, LUL, RS, SLL and VGR) was used. PAS has practically complete coverage, although there is a varying quality in registration of diagnosis and procedure codes in these registers.

Data was retrieved from the regions on all adult patients (>18 years) with an acute stroke diagnosis, defined by ICD-10 codes I61* for ICH and I63* for IS as main diagnosis in the time-period from 2007 to 2012. All data for these patients during this time period was extracted and the individuals were linked to data retrieved from Riksstroke. Data on healthcare contacts, procedure codes and comorbidities was used for paper IV and V.

3.2.3 LISA database

Statistics Sweden (SCB) collects population based data which can be used for research purposes. From the LISA database (Longitudinal integration database for health insurance and labour market studies), information on each individual's socioeconomic status can be retrieved. The database presently holds annual registers since 1990 and includes all individuals 16 years of age and older who were registered in Sweden as of 31st of December for each year. The database integrates existing data from the labour market, educational and social sectors and is updated each year with a new annual register.

Data on socioeconomic factors was linked on individual level to the study population of stroke patients. Data on socioeconomic status was used in paper IV to allow for case-mix adjustment.

3.2.4 Total population register

Statistics Sweden keeps information on date of death as part of the total population register (RTB). This information was linked on individual level to the study population, and used in papers IV and V.

3.2.5 Care and social services for the elderly and for persons with impairments (SoL)

The SoL register is administered by the National Board of Health and Welfare (Socialstyrelsen). The register contains information on individual level on the scope of

municipal services in accordance with the Social Services Act (2001:453), provided for elderly and persons with functional impairments.

Data on special forms of housing (measured in days for paper V and proportion moving into special housing in paper IV) and home care services (measured in hours) was linked on individual level to the stroke study population and used in paper IV and V.

3.2.6 MiDAS database

The MiDAS database is administrated by the Swedish Social Insurance Agency (Försäkringskassan) and contains information on individual level about sick leave (after first two weeks of absence), rehabilitation support and disability pensions / early retirement.

Data on sick leave (measured in net days) and disability pensions / early retirement (measured in net days) was linked on individual level to the stroke study population and used in papers IV and V. In paper IV this information was used as a health outcome indicating the proportion of patients who were working full time after one year, as a proxy for regaining work ability, whereas in paper V it is assessed as a resource in days of work absence.

3.2.7 Study populations and variables

The final study population for paper IV and V consisted of patients registered both in PAS and Riksstroke, linked to each other and other register sources through the unique Swedish personal identification numbers. Data linkage and de-identification of the dataset was performed by Statistics Sweden. Extensive data management was performed to ensure consistency between the data from the different PAS systems and identification of variables necessary for the analyses in papers IV and V.

Patients residing in another region than the seven included regions in study IV and V were excluded from the analysis to allow for complete follow-up (although the initial stroke care was received in one of the included regions). The final study populations for each study were:

- The study population for paper IV consisted of 14,125 patients acquiring a stroke (IS or ICH) during 2010, allowing inclusion of two years of history (enabling case-mix adjustments) and two years follow-up (only one-year results presented in paper IV).
- The final study population for paper V consisted of 47,807 patients diagnosed with a stroke (IS or ICH) during 2007-2010, allowing for two years follow-up.

A summary of the study variables from each register for papers IV and V are listed in Table 5. Baseline characteristics in paper IV were used for case-mix adjustment of the results whereas in paper V they are used to stratify the patient population (by stroke type and age) and to give descriptive data of the study population.

Table 5. Study variables for paper IV and V

	Paper IV	Paper V	Register source
<i>Baseline characteristics</i>			
Stroke type	X	X	PAS
Age	X	X	PAS
Sex	X	X	PAS
Level of education	X		LISA
Born outside the EU	X		LISA
Single household	X		Riksstroke
Living arrangements	X	X	Riksstroke
ADL dependency prior to stroke	X	X	Riksstroke
Prior stroke within 2 years	X	X	PAS
Atrial fibrillation and/or hypertension diagnosed within last 2 years	X		PAS
Level of consciousness at arrival to hospital	X		Riksstroke
<i>Health outcomes</i>			
Survival	X	X	RTB
Recurrent stroke	X		PAS
Functional disability (mRS)	X ¹	X	Riksstroke
Good general health	X		Riksstroke
Work ability	X		MIDAS
<i>Resources</i>			
Inpatient bed days	X	X	PAS
Outpatient visits, speciality care	X	X	PAS
Outpatient visits, primary care	X	X	PAS
Home care service (hours)	X	X	SoL
Special housing	X ²	X ³	SoL
Work absence (days)		X	MIDAS

ADL dependency is defined as being dependent on help with dressing and/or going to the toilet.

1. good outcome; 2. proportion moved into special housing; 3. days

3.3 METHODS

3.3.1 Health economic analyses

Papers I-III were designed as economic evaluations where cost-utility analyses were performed. In order to enable combination of several data sources and projecting the long-term cost-effectiveness of treatments for RA, Markov cohort models were used. In paper I, a Markov cohort model was developed and analyses performed on one first-line biological treatment alternative compared to no treatment. In paper II, the model was further developed to include several treatment options as first-line biological treatment, but also include second-line treatment options. In paper III, a comparison between different patient populations and data sources (register vs RCT) was conducted, putting larger emphasis on methods of

matching patients and the impact of assumptions made in the model and in relation to the data.

Papers IV-V were designed as burden-of-illness studies using an incidence based approach, estimating the burden bottom-up based on register data from multiple data sources. In paper IV, health outcomes and resources were defined in measurable units and advanced statistical analyses were performed to assess any differences between hospitals, after adjusting for patient mix. This paper is not a classical burden-of-illness study, although the components measured are part of this methodology. The way the results are presented may be considered closer to the framework of performance measurement, where the indicators of interest usually are structure, process or outcome indicators (95). However, for this thesis, the aspects closer to health economic theory are in focus instead. In paper V, the costs were estimated from the identified resources, and summarized by functional disability and stroke type, allowing for use of the results in future health economic evaluations.

3.3.2 Markov models

A Markov cohort model was developed for enabling cost-effectiveness analyses in papers I-III. The model was based on earlier models of infliximab (93) and etanercept treatment (96), adapted to accommodate register data and including a second-line biological treatment option as in paper II, as well as allowing for comparison between more than two treatment options.

Health states in the model were stratified over five mutually exclusive states of functional status (measured with HAQ), each separated into two states of disease activity (high/low, measured with DAS28). The cut off points for the HAQ states were 0.6; 1.1; 1.6 and 2.1 whereas the cut-off for high disease activity was set at DAS28>3.2. The model had a long-term horizon (20 years) and the cycle length was set to 1 year. In each cycle, patients could continue or discontinue treatment, remain in their current health state, transit to adjacent health states or die (see Figure 6). The model had in all 15 possible health states (plus dead).

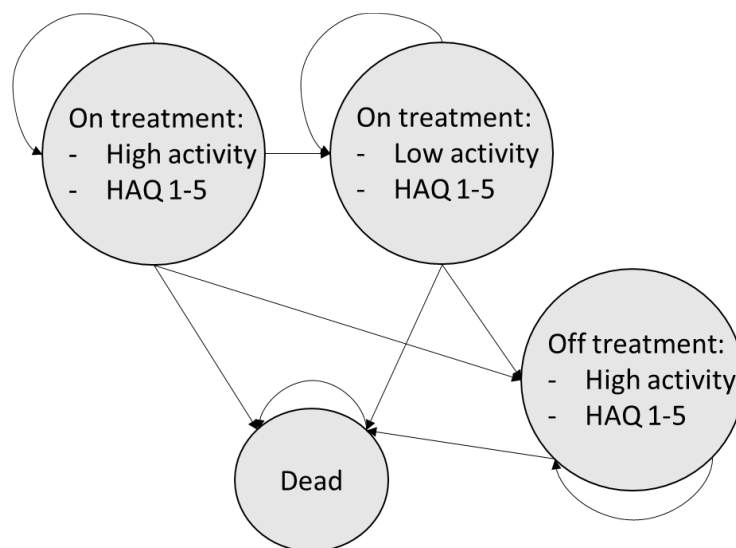


Figure 6. Simplified model structure used in paper I-III

The transition probabilities in the comparator arm, that is disease progression without biologic treatment, as well as mortality rates, costs, and utilities were based on published literature. The analyses had a societal cost perspective including both indirect costs and cost in added life-years as recommended for Swedish reimbursement submissions at the time of this study.

For paper III, three patient cohorts were identified and included in the model: the patients included in the infliximab trial (ATTRACT), patients initially treated with infliximab and registered in SRQ (Stockholm) and a subset of these register patients meeting inclusion criteria for the ATTRACT trial. The two data sources (trial vs register) had different characteristics in relation to efficacy data as they had different time-horizons (duration of trial vs data over 10 years) and possibility of comparators (placebo vs “no treatment”), imposing different needs of assumptions for enabling the economic evaluation. Two sets of assumptions were therefore applied in the model on each of the three cohorts (Table 6).

Table 6. Model assumptions related to effect data

	Assumptions made in the Markov model	
Aspect	ATTRACT assumptions (RCT data)	STURE assumptions (Register data)
Comparator	Placebo arm of the trial	HAQ progression on standard therapy from published literature (0.065 HAQ/year)
Discontinuation of treatment	All patients discontinue treatment after 1 year	Continuous discontinuation function based on observed discontinuation rates in the register
Reverting to baseline HAQ at discontinuation of treatment	Assumed	Not assumed

All results for studies I-III were presented as ICERs, interpreted as cost per QALY gained, and extensive sensitivity analyses were performed to assess the uncertainty in assumptions made and uncertainty in the underlying data. Both deterministic and probabilistic sensitivity analyses (PSA) were performed. In the PSAs, 1,000 runs were performed to assess the precision in the estimates. Dirichlet distributions were assigned to the HAQ transitions in the initial year as it is suitable to estimate the uncertainty in probabilities when using rival events (five mutually exclusive HAQ events in the model), and beta distributions were assigned to the DAS28 transitions as it is suitable when using probabilities between 0 and 1.

The software TreeAge was used for modelling in papers I-III.

3.3.3 Statistical analyses

In papers I-III, a regression function based on the RA-register dataset was implemented in the Markov model to assess the probability of discontinuing treatment each year (i.e. in each cycle in the model). The probability of discontinuing treatment with any anti-TNF therapy was higher in the initial year of treatment than in subsequent years, irrespective of whether it was taken as a first or second biological treatment. The discontinuation function was therefore separated into two parts in the model to get a better fit to the data; a logistic function for the first year and a Weibull survival function for subsequent years.

The probability of discontinuing therapy increased with VAS pain at baseline (first biological in first year), HAQ at baseline (first biological in subsequent years), initiating treatment with an anti-TNF therapy after 2003 (first biological in first year), age at disease onset (second biological in first year) and DAS28 at baseline (second biological in subsequent years), which were accounted for in the model.

In paper IV, an adjustment of differences in health outcomes and resource use was employed, using a multivariable fixed-effects regression model adjusted for clustering of patients within clinics. Logistic regression was performed for dichotomous outcomes, while continuous data was analysed using ordinary least squares (OLS) regression. The models included predictors of sociodemographic factors, health profile at baseline and stroke characteristics. The case-mix adjusted results indicate the hospital effect on each dependent outcome (referred to as adjusted results).

The software STATA 13.0 was used for statistical analyses.

3.3.4 Costing

None of the registers used for this thesis provided data on costs, but rather on resources. For cost estimations, necessary for papers I, II, III and V, each unit of resource was multiplied by a unit cost.

In papers I-III, cost of treatment was estimated by using the unit costs for the anti-TNF therapies from the Swedish Pharmacy List prices (FASS) as well as cost of administration in the case of infliximab therapy. Other direct and indirect costs in these papers were based on published literature (53, 96).

In paper V, the direct and indirect costs of stroke were estimated. The unit costs of inpatient stay and outpatient visits in specialist care were retrieved from the cost-per-patient (KPP) database at The Swedish Federation of County Councils (SKL) (97). First-year cost of inpatient care (per day) was identified from the KPP-database for patients with main diagnosis ICD-10 I61* and I63*, for ICH and IS respectively. Unit costs of inpatient care during second year as well as unit costs for outpatient visits both years were estimated by an unweighted average of daily cost in a general ward, acute care, palliative care, internal medicine, stroke care, geriatric care and rehabilitation. The cost of primary care visits was estimated by an average of available regional price lists, using rates for medical doctors and

other healthcare professionals respectively. Home care services and cost for special housing were retrieved from the cost-per-user (KPB) database at SKL (98). An unweighted average cost of the reporting municipalities was used.

Indirect costs were estimated based on days of absence from work, defined as either on sick leave or with disability pension, using a human capital approach (50). The cost of work absence was estimated based on average monthly wage of all sectors, published by Statistics Sweden, plus employer taxes.

3.4 ETHICAL CONSIDERATIONS

The studies have been approved by the regional ethical committee board at Karolinska Institutet, Stockholm (dnr 2008/352-31 for the studies on RA and dnr 2013/1541-31/5 for the studies on stroke).

Register based studies contain sensitive data on patients' health and well-being. In these studies, only de-identified data (without personal identification numbers) was accessible and the data was kept in a secure setting. Furthermore, data is only presented on aggregated level to ensure that patients are not identifiable in the presented results. The potential harm on patients' lives is deemed to be minor whereas the increased knowledge of the health economic aspects of these diseases may serve as a knowledgebase for better and more cost-effective use of healthcare resources in the future, which will benefit patients as well as society at large.

4 RESULTS

4.1 COST-UTILITY ANALYSIS OF ANTI-TNF TREATMENT FOR RA (PAPER I & PAPER II)

Register data from the SRQ was used to model the cost-effectiveness of anti-TNF use in Swedish clinical practice. Paper I only assessed infliximab as first-line treatment and paper II evaluated etanercept alone and all anti-TNFs combined (either as monotherapies or in combination with MTX), both as first and second-line biological treatment.

In all, the results from these papers indicated that as the anti-TNFs have been used in Swedish clinical practice, it has been used in a cost-effective manner on a macro-level for first-line treatment. The base case scenario produced ICERs of €22 – 54,000, dependent on sub-population analysed for the combination regimens (i.e. combination of anti-TNF and MTX). The results further indicated a lower cost-effectiveness ratio for first-line biological treatments than second-line. For second-line biological treatment, the results were not as clear on macro level, rather cost-effective use of these therapies was primarily seen in those with high underlying disease progression.

The results indicated that the rate of progression in the comparator arm was of greatest importance for the cost-effectiveness results. The rate of progression for the comparator was based on published literature as it was not available in the register. At the time of the two different papers, there was no consensus in literature regarding the actual rate of progression in absence of anti-TNF therapy, instead it ranged between 0.03 – 0.13 HAQ / year in different publications. At the time of publication of paper II, more studies had been published supporting a lower value than used in paper I (which was 0.065 HAQ/year). A threshold analysis was therefore performed as part of paper II, which indicated a cut off point for cost-effectiveness at a rate of progression without treatment at 0.045 HAQ points/year (i.e. exceeding this would give a cost-effective result), illustrated in Figure 7. The results from these analyses indicated that it is more cost-effective to treat patients with higher rates of underlying disease progression.

The results were also sensitive to age at initiation of anti-TNF therapy. This is driven by the effect these therapies have on maintaining work ability, decreasing the indirect costs associated with RA. As patients above 65 are assumed not to work, this benefit is not accounted for in the analysis of an older age group.

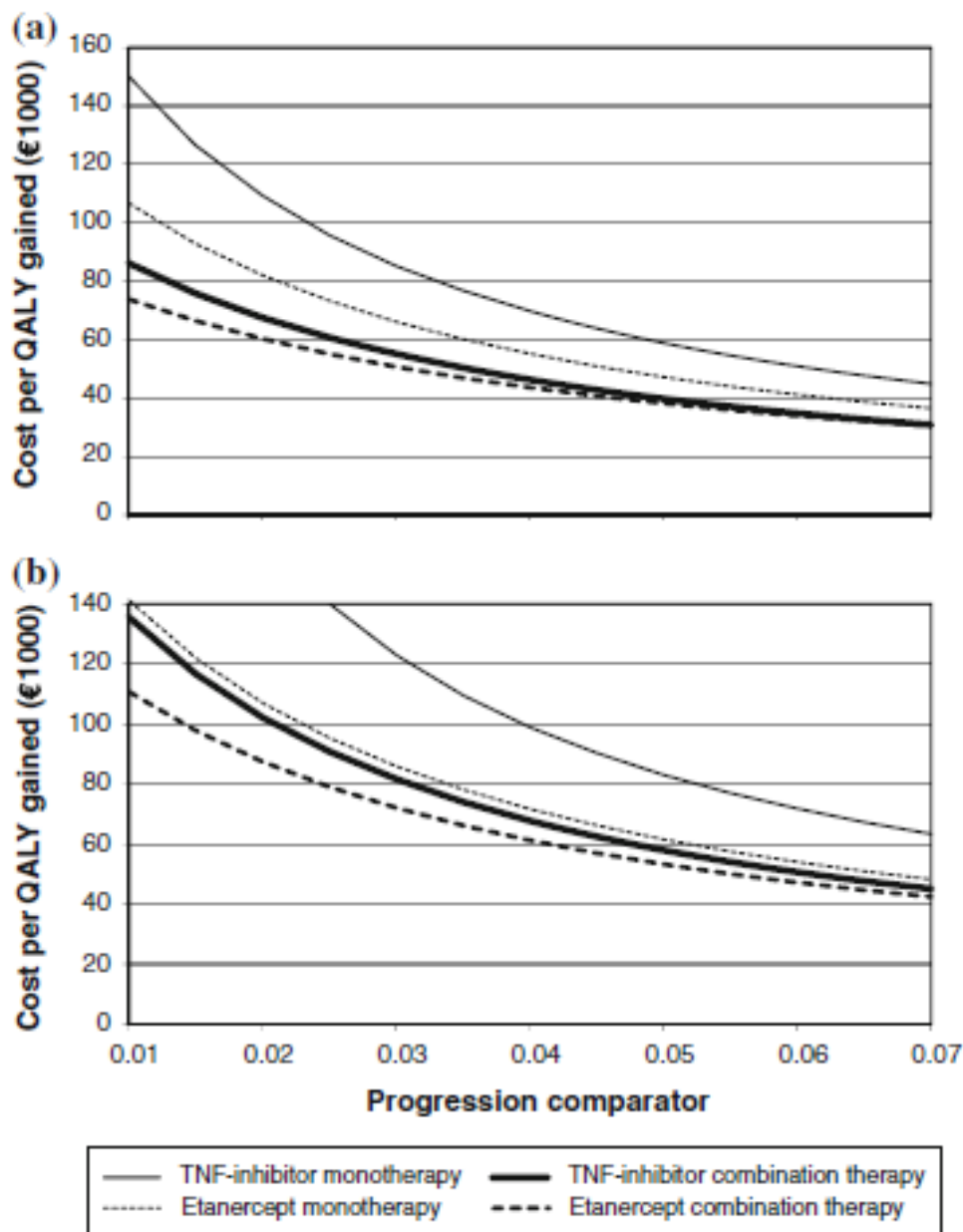


Figure 7. Cost per QALY gained at different progression rates of the comparator for the first (a) and the second (b) biological treatment received

4.2 EVALUATION OF REGISTER- VS RCT-BASED COST-UTILITY ANALYSIS OF ANTI-TNF TREATMENT FOR RA (PAPER III)

An early model based on phase III RCT data on infliximab concluded that it was a cost-effective therapy for RA (93). The results from paper I indicated that infliximab had been used cost-effectively in Swedish clinical practice. In paper III, the precision of the predictive cost-effectiveness assessment based on a phase III trial was evaluated with the use of register data from the SRQ. This was performed on infliximab therapy, as data from both the phase III trial and the Stockholm part of the SRQ (STURE) were available.

The results indicated that approximately half (48%) of the patients receiving infliximab therapy in clinical practice would have been eligible for inclusion in the pivotal phase III trial.

This population constituted the matched population from the registry. The other two cohorts were the registry cohort and the RCT cohort.

The results for the three patient cohorts ranged from cost saving to €2,400/ QALY gained, and a range of €24,900 to €26,000 /QALY gained when the ATTRACT and STURE assumptions were used, respectively. Sensitivity analyses indicated that the inclusion of placebo effect had the largest effect on the results, increasing the cost per QALY gained to approximately €50,000 for all patient cohorts.

The results further indicated that the treatment effect of infliximab measured in clinical trials and clinical practice resulted in comparable cost-effectiveness ratios, as calculated by using a modelling approach, whereas the assumptions made in relation to the effectiveness data and the chosen comparator had a large impact on the results. Within each set of assumptions, the different cohorts produced similar results also after probabilistic sensitivity analysis (see Figure 8).

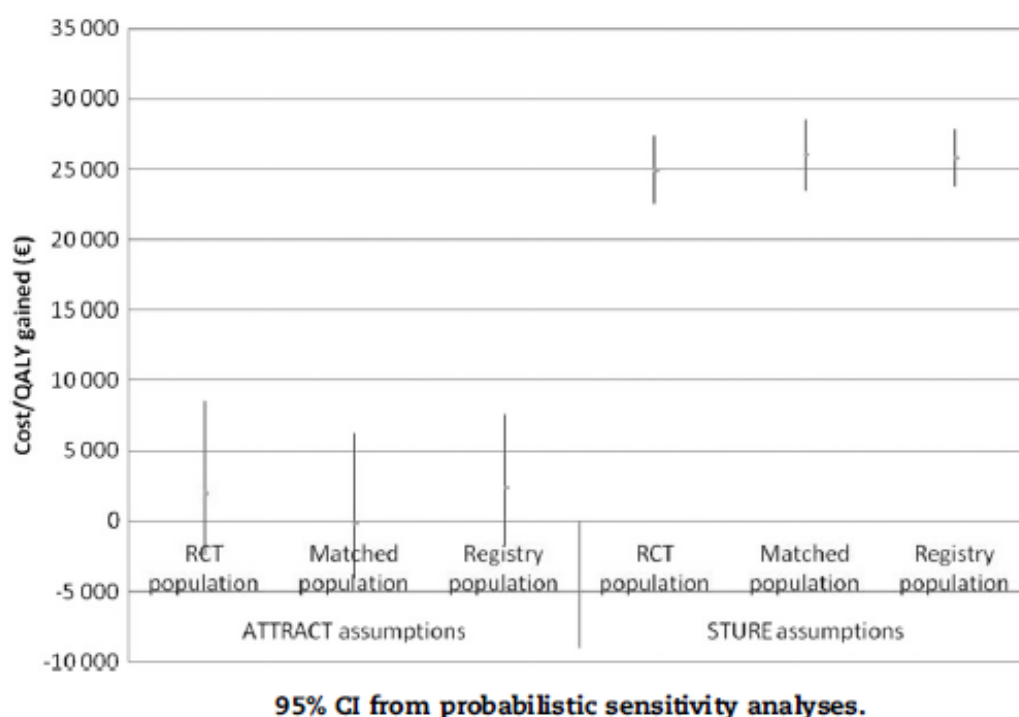


Figure 8. Results from probabilistic sensitivity analysis comparing three different cohorts and two sets of assumptions in relation to the effect data

4.3 HOSPITAL COMPARISON OF STROKE CARE (PAPER IV)

Paper IV estimated health outcomes and resource use one year after stroke, and presented a comparison of performance between hospitals and regions while accounting for differences in patient mix.

The results indicated that the remaining effect one year post-stroke on different aspects of health outcomes was substantial; 26% of the patients had died, approximately 5% had a recurrent stroke and almost 40% of the survivors had remaining functional disability. Still,

75% of the surviving patients had rated their general health as good. The results further indicated substantial use of healthcare resources. The use of county council resources amounted to 22 inpatient bed days and 23 outpatient visits (speciality care and primary care combined) on average. Additionally, the use of municipal social services amounted to 151 hours of home care service and 13% of the population living in special housing, on average one year post stroke. The variations between hospitals in these estimates were large. The confidence intervals of the crude rates on hospital level indicated that there were statistically significant differences between hospitals, and several hospitals had significantly lower or higher crude rates than the patient-level average of the whole study population. Variations were also identified between hospitals within the same region.

The results indicated that there were significant differences in health outcomes between hospitals also after adjusting for patient mix (Figure 9). Six hospitals performed better in terms of health outcomes (marked with light green) and six hospitals performed worse (marked with light red) compared to the other hospitals, with statistically significant deviation on several indicators for health outcomes.

Regarding resource use, there were also significant differences in the adjusted comparison between hospitals (Figure 10). The range of inpatient stay spanned from -8 days to +16 days compared to the mean, and the corresponding differences for outpatient visits spanned from -7 visits to +7 visits for speciality care and -10 to +21 visits for primary care. There were also substantial deviations for municipality care.

Most hospitals showed a pattern with higher levels of resources of one kind (e.g. inpatient care) and lower levels of another (e.g. outpatient care or special housing). However, five hospitals had lower levels of resources use (marked with light green) and five hospitals had the opposite results; higher levels of resource use compared to the other hospitals (marked with light red). Within regions, trends could be identified with regards to the division of outpatient visits between specialist and primary care; e.g. lower number of primary care visits whilst higher levels of specialist care as in RS, and the opposite relationship as in VGR.

Differences in health outcomes and resource use between hospitals for patients with stroke were substantial and not entirely explained by differences in patient mix. No conclusions can be drawn as to which resource type provided the best health outcomes, and no clear relationship between resources and health outcomes was detected. However, a few hospitals had both worse health outcomes and more resources, implying a less cost-effective healthcare delivery or value of care.



Figure 9. Adjusted deviation in health outcomes one year post-stroke. Patients with a stroke in 2010. Colour markers indicate better (green) or worse (red) health outcomes if having significant deviations in only one direction for at least three indicators of outcome. Exception was made to “full-time work ability”, as this variable concerned a sub-population and the data used were based on sick leave, which is only a proxy for work ability.

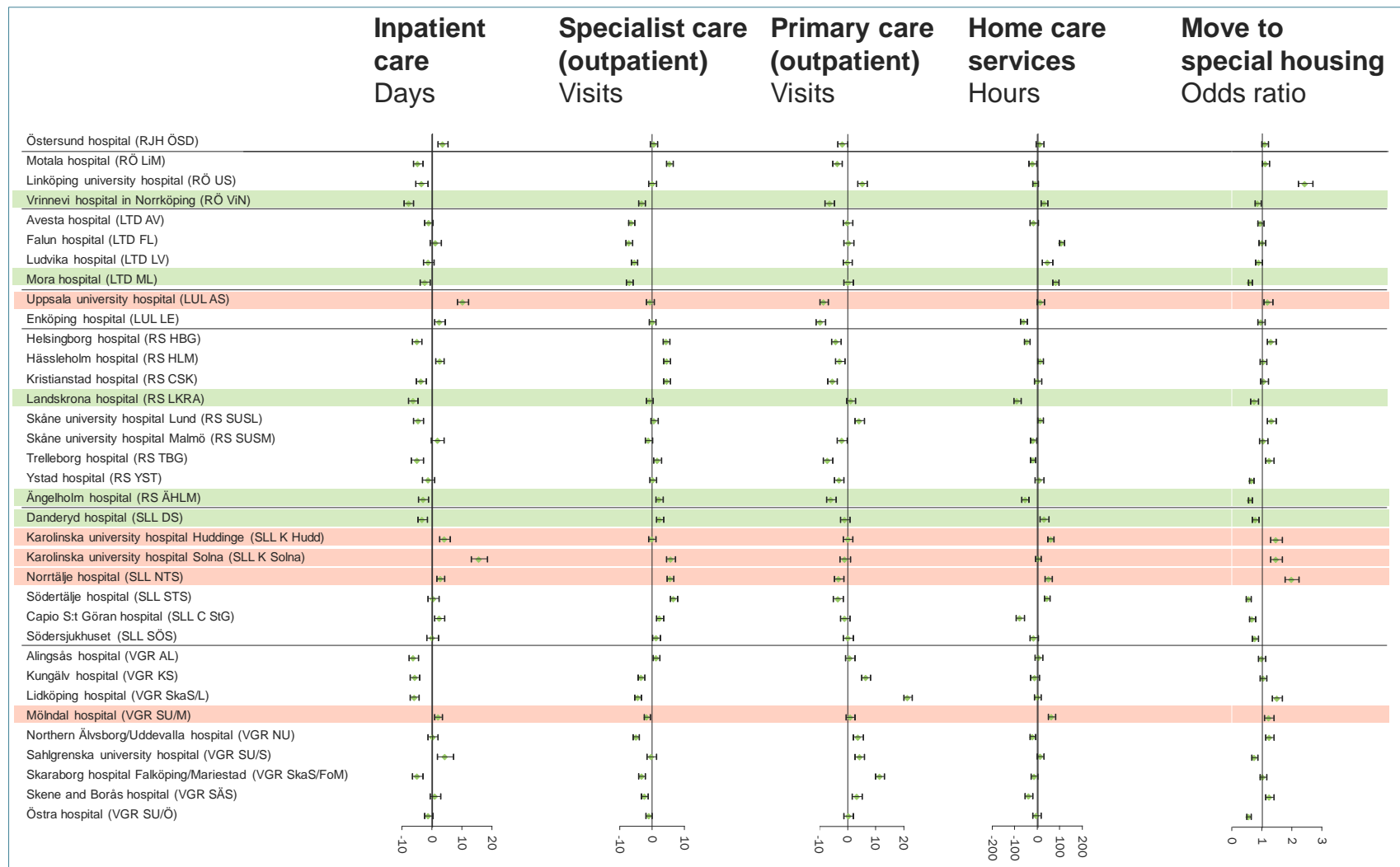


Figure 10. Adjusted deviation in resource use one year post-stroke. Patients with a stroke in 2010. Colour markers indicate higher (red) or lower (green) level of resources, highlighted in cases where there was a significant deviation of “inpatient care” and “move into special housing” in only one direction. Limitation to these two variables was done in accordance with findings in paper V which demonstrated that these two resource items are the main drivers of the total costs of stroke care

4.4 COST OF STROKE BY FUNCTIONAL DISABILITY (PAPER V)

Paper V estimated the total costs of stroke, stratified by functional disability and stroke type up to two years post-stroke.

The total per-patient cost during first year for all patients was approximately 470,000 SEK/€50,000 and 370,000 SEK/€39,000 for patients with ICH and IS respectively. The corresponding costs for the second year were 420,000 SEK/€45,000 and 350,000 SEK/€37,000. Indirect costs constituted 12-20% of the total costs dependent on years passed after stroke and stroke type.

The results indicated a relationship between level of functional disability and cost during both the first and the second year following the stroke (Figure 11). During the first year, costs increased with each level of functional disability, and patients with ICH were associated with higher total average costs for any level of functional disability (apart from dead) compared to patients with IS. These cost differences were primarily driven by the differences in use of inpatient care and special housing. The total average cost ranged from 200,000 SEK/€21,000 to 1,100,000 SEK/€120,000 for the first year following a stroke, for the different patient sub-groups. mRS 5 was associated with an almost four-fold increase in costs compared to mRS 0-2 for patients irrespective of stroke type.

The results further indicated that there were remaining costs for stroke patients in the second year after stroke, especially for patients with continuous functional disability (mRS 4 and mRS 5). ICH was still associated with higher costs for most groups as well as in total, although with a smaller difference to IS than for the first-year costs. The cost increase of mRS 4 or 5 compared to mRS 0-2 in the second year was approximately eight-fold. For the second year after stroke, the costs of municipality resources were the main drivers of total costs.

Stratified analyses by age indicated that for any given age category, there was an increase in total costs for each level of functional disability during the first and second year, although being in the worst state of functional disability (mRS 5) was associated with slightly lower costs than mRS 4 during second year for older age groups (see Figure 12 for IS patients as example). Further, the youngest age group was associated with the highest cost, irrespective of level of functional disability during the initial year. This was primarily driven by higher levels of indirect costs and inpatient stay at worse levels of functional disability.

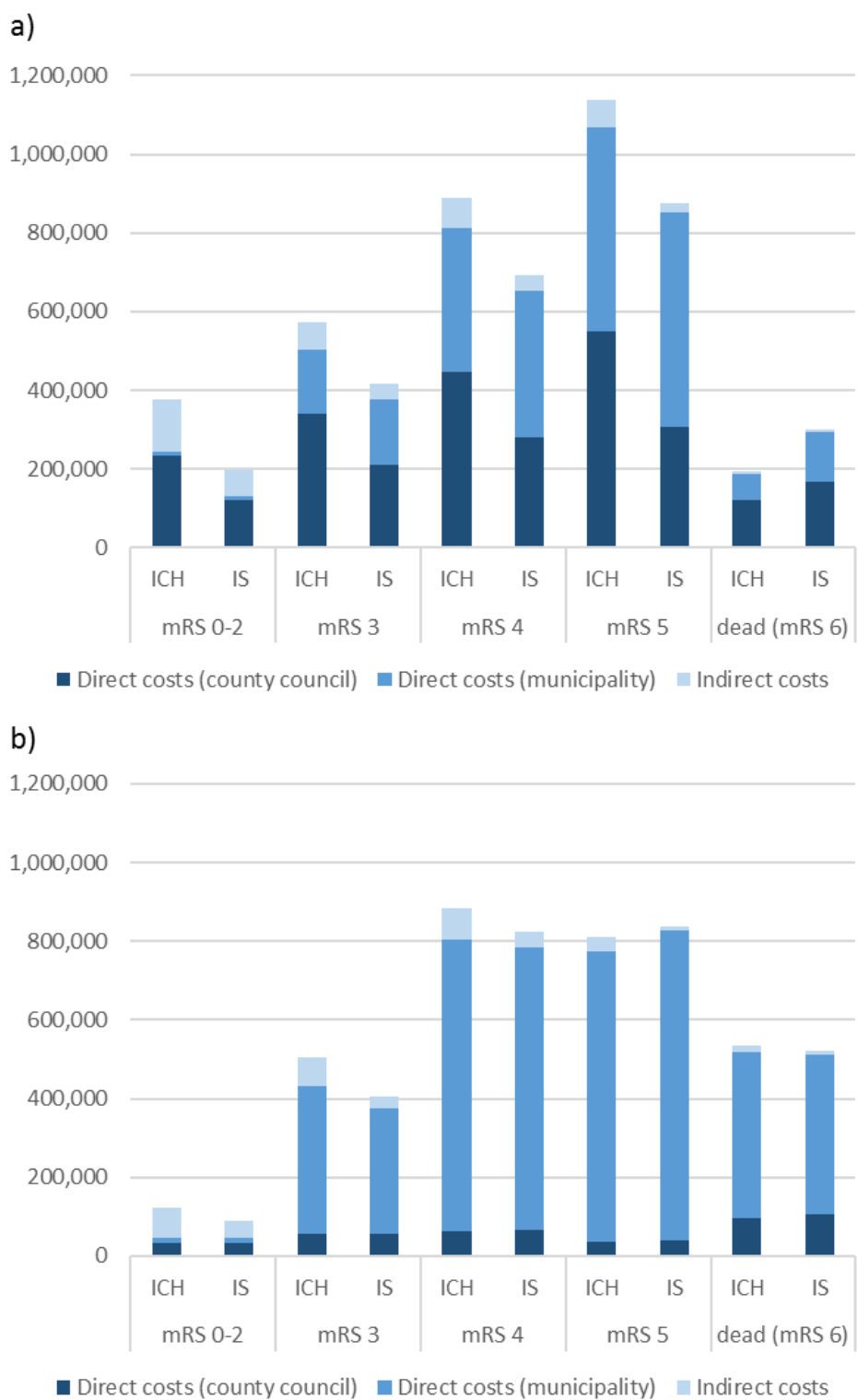


Figure 11. First (a) and second (b) year cost by functioning ability and stroke type, per patient

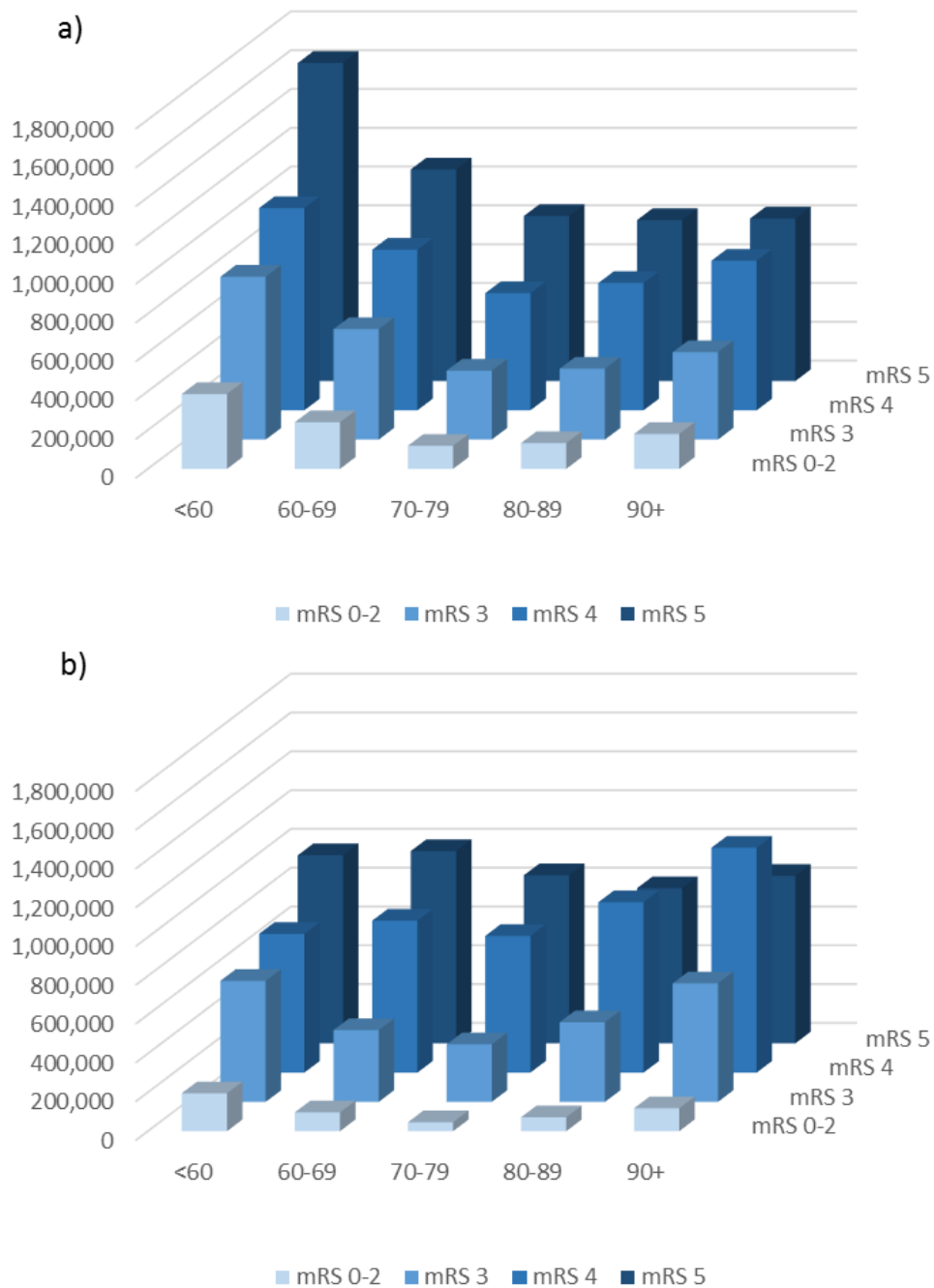


Figure 12. Total cost (SEK) by functional disability and age during first (a) and second (b) year post ischemic stroke

5 DISCUSSION

5.1 STUDY FINDINGS

The findings of the papers in this thesis have provided valuable insights into the health economics of RA and stroke and the use of quality register data in such assessments.

The results from papers I and II indicated an overall cost-effective use in clinical practice of anti-TNF therapy for RA as first-line therapy on macro level in Sweden, compared to a scenario of no biological treatment. The results were, however, sensitive to the underlying disease progression in the absence of biological treatment. Almost all therapies investigated have provided good societal value for the money (in Sweden) at a progression of 0.045 HAQ points per year for the comparator. Hence, the underlying disease progression of each individual patient is of importance for cost-effective use of therapies. Data from the SRQ were used for effectiveness of anti-TNF treatment over HAQ and DAS28 categories, as well as discontinuation rates, providing valuable information on the use and effect of treatment in clinical practice.

There are pros and cons with register data and RCT data, and views on which data source is more reliable and more appropriate in health economic analyses are not coherent. Paper III demonstrated that the effectiveness data from two different types of sources give comparable incremental cost-effectiveness estimates when the same comparator was used and the same assumptions were applied to the data and model. This was demonstrated with the example of infliximab treatment for RA. Although only half of the patients receiving infliximab therapy in clinical practice were found eligible for inclusion in the phase III clinical trial, this did not translate into any major difference in cost-effectiveness results. Early economic evaluations based on RCT data are valuable but caution needs to be taken to the comparator used and assumptions made if the results are to be used as predictions for cost-effectiveness of a new therapy in clinical practice and used for policy decisions. In addition to the data used from SRQ in papers I and II, SRQ data provided valuable information on patient characteristics, enabling matching of the patients to RCT inclusion criteria.

Paper IV demonstrated that the impact of stroke on health outcomes and resource use was substantial, and that differences in these stroke-related indicators between hospitals were not entirely explained by differences in patient mix, indicating geographical inequalities in Swedish stroke care. Healthcare organization of regions and other structural features, could potentially explain parts of the differences identified. No clear relationship between resources and outcomes were detected in this paper, indicating that there is potential in ensuring more cost-effective use of current resources. As consequences of stroke are life-long for many patients, (although only estimated for the first year in this study), the total effect for the patients and society at large is likely to be even larger than demonstrated in this study. The results further highlighted the importance of including a wide range of both health outcomes and resources in studies of stroke, as this is a necessity if conclusions are to be drawn on the total effects of stroke. Data from Riksstroke on health outcomes and patient characteristics

(important for case-mix adjustment) were used for this paper, including PROMs that has been collected by Riksstroke.

The costs following a stroke were extensive during the first year and beyond, as indicated by paper V. The results of this paper indicated increasing costs with worse functional disability, and higher costs for patients with ICH compared to IS during the first year after stroke.

Further, the results indicated higher costs for lower age groups, driven by indirect costs and more inpatient care than for older patients. The results also demonstrated the importance of having a scope beyond the healthcare budgets when assessing the costs of stroke, specifically highlighted by the more long-term costs of municipality financed care identified in the results. Riksstroke provided data on level of functional disability, enabling stratification of costs.

The papers of this thesis have highlighted diverse possibilities of using quality register data in health economic analyses for diseases associated with a chronic condition. It has been shown that data from quality registers can provide valuable information when:

- Assessing the real-life effectiveness of therapy, which through health economic modelling have given indication of its cost-effectiveness in clinical practice
- Evaluating the predictive RCT assessment as well as the impact of different patient populations on the cost-effectiveness results
- Assessing health outcomes and putting them in relation to resource use, as well as enabling comparison of hospital performance
- Assessing resources and costs by level of functional disability

5.2 CRITICAL EVALUATION OF STUDY METHODS

All papers in this thesis were based on register data which is associated with both strengths and limitations.

A major strength was that the registers used all have good coverage of the Swedish RA and stroke populations from the covered geographical regions of the papers, minimizing the risk of selection bias in the study populations. Still, as none of the studies had national coverage, caution should be applied to generalizing the results to other regions in Sweden or to other countries. The registration of a patient into a quality register is not automatically performed from the medical record, instead it requires manual registration of specific variables after diagnosis. This procedure ensures that only patients with confirmed correct diagnoses are registered in the quality registers whereas there is an over registration of diagnoses with RA or stroke in the patient administration systems. The study populations were based primarily on the data from the quality registers, ensuring only patients with confirmed diagnoses were included in the assessments of this thesis.

In papers IV and V, several registers were linked to each other by using the Swedish personal identification number, allowing for a more holistic approach to the health economic analyses in these papers. This bottom-up approach of using register data allows for large datasets to be

included in the analysis which strengthens the statistical stability of the results, is less costly and more time-efficient than performing a primary data collection from the patients. The size of the study populations were also large enough to perform sub-group analyses and stratifying the patient population for the different analyses. However, not all resources could be assessed using this methodological approach, for example information on informal care, pre-hospital care, municipality-financed home healthcare (performed by medical staff) or detailed information on rehabilitation received were not available in the registers and hence not assessed.

Register based studies are also associated with common limitations that need to be considered when interpreting the results, such as incorrect registrations, missing data or incomplete data. When performing data management on the datasets, corrections were made to incorrect data to minimize the impact of this limitation. This was however only done in cases where there was a logical maximum or minimum value (e.g. maximum value of 365 inpatient days during one year). No other adjustments, like for example imputation of missing data, were performed. Missing data may have an impact on the results if the patient population with missing data differ from those with complete data. In cases where the coverage of a variable was too low, the variable was instead omitted from the statistical analyses in order not to lose these patients in the statistical models. In paper IV, for example, data on stroke severity by National Institutes of Health Stroke Scale (NIHSS) was omitted for this reason.

Additionally, the quality of registrations for healthcare contacts in PAS (e.g. primary care diagnoses) differed between hospitals and regions, introducing a systematic error when assessing differences between hospitals and regions as in paper IV. To minimize the impact of this, the total number of resources utilized were studied in both paper IV and V (not only stroke-related). The greater part of the healthcare resource use was nevertheless found to be stroke-related in a sensitivity analysis in one of the regions with a high frequency of reporting of diagnosis codes. This sensitivity analysis indicated that applying a definition of ICD-10 codes directly related to stroke (acute or sequelae codes) would underestimate the resource use, as many healthcare contacts had codes likely related to consequences of stroke (e.g. eye exams and speech difficulties) but without a complementing stroke-specific code. Another option would have been to adjust for pre-stroke resource levels when assessing resources post-stroke, in which case the patients would act as their own controls. This approach requires defining a time frame prior to stroke assessed as baseline and a strategy on how to handle patients who die, as these patients may incur less resources after a stroke than prior to the stroke. A sensitivity analysis performed for paper V also indicated that resource use increased the months just prior to the stroke, which may actually be related to the upcoming stroke event. An additional option would have been to compare the resources to a matched control group from the general public. However, such data was not available within the scope of the larger Sveus-program that this study was a part of. In paper IV, the case-mix adjusted comparison of resources between hospitals were adjusted for pre-stroke inpatient bed days as a proxy for comorbidities and how resource demanding the patient population was prior to the stroke. In paper V on the other hand, resource use was stratified based on functional

disability (by applying an approximation of mRS), enabling the use of mRS 0-2 (good functional ability) as reference population in assessing increasing costs with worse functional disability post stroke. Still, it should be noted that although the transformation to mRS from variables in Riksstroke is validated (94), it does not provide a distinction between mRS 0, 1 and 2 as in the original mRS instrument. The results based on functional disability in this study may nevertheless provide deeper insights and input when assessing healthcare interventions post stroke (in e.g. health economic modelling). However, for assessments of preventive interventions a comparison needs to be made to the pre-stroke resources and costs.

Health outcomes were retrieved from several sources and consist of a mixture of hard endpoints and patient-reported outcome measures, the latter dependent on participation of patients and their ability to answer the questions. For some stroke patients, these questions were completed by their next of kin, possibly rendering other results than if the patient would have answered the questions themselves. These patients were most likely severely impaired after stroke, which may give rise to systematic errors. It is however unlikely that such errors differ between hospitals or regions, and impact on the conclusions in paper IV are expected to be minor.

In all comparative studies or economic evaluations, it is important to ensure that the comparisons made are based on equivalent patient populations to be able to draw any conclusions from the analyses. In papers I-III a comparator arm of no biological treatment was included in the economic evaluations of anti-TNF treatment, to enable comparative analyses. However, when using register data for assessing the cost-effectiveness of interventions, there is a challenge in choosing a comparator population for the analysis. The comparative scenario needs to be conducted for the same population as the evaluated treatment alternative, ensuring that only the effect of the treatment is evaluated and that no differences in patient populations are incorporated in the analysis. The patients in the comparator arm needs to be matched to the ones receiving therapy. However, as a therapy is introduced to the market and becomes the new standard, the patients who receive the therapy will not be similar to those not receiving it, because of contraindications or other reasons. Hence, a matched comparator group is simply not available in the register. Alternatively, historical data could have been used (before introduction of the new therapy) for comparison. However, this may not be entirely representable as other advances in healthcare over time may also influence health outcomes or resource use (e.g. better diagnostics, other treatments, routines for visits etc.), therefore altering the results. For the economic evaluations in papers I-III, historical data from the register was not available and hence not a possibility for these assessments. Instead, progression for the comparator arm was based on published literature, choosing estimates based on populations as close as possible to the indication of anti-TNF therapy (i.e. failed two conventional DMARDs). In paper III, a matched cohort was identified from the register dataset to assess one patient population in real life that was similar to the population included in the RCT.

Another alternative to using a comparator of no biological treatment would have been to compare the anti-TNFs to each other in papers I and II. Such an analysis would have to account for differences in the patient populations due to patient/physician preferences for the therapy/mode of administration (and also potentially the clinical budget impact), which may impact the choice of therapy. Additionally, the different therapies became available at different points in time which may affect behaviour (e.g. possibility to switch to other therapies, increased experience with therapies) and patient mix (more severe cases for the biological DMARDs first introduced to the market). However, TLV has concluded that there is no significant difference in effectiveness and adverse events profile of these therapies and any comparison between the different anti-TNFs comes down to cost-minimization in the absence of a head-to-head trial (www.tlv.se).

In papers IV and V, there was no evaluation of one intervention compared to another. Still, comparability between different populations were necessary to account for in a proper way. In paper IV, comparability between hospitals was ensured by adjusting the results for differences in patient mix. However, not all aspects of the patients' conditions could be controlled for because of lack of data, for example time to hospital (important for acute treatment of stroke) which was simply not available. Additionally, stroke severity data (NIHSS) is collected within Riksstroke and has been shown to be important for predictions of outcome (99), but NIHSS had too low coverage for the study population in paper IV to be included as a case-mix variable. Level of consciousness, which has been shown to be a strong predictor for outcome and also a good approximation of the full NIHSS in predictions (100), was however included whereby this limitation should have minor impact on the overall conclusions. In paper V, sensitivity analyses were performed by stratifying the estimated costs by age as well, to assess the impact of another potentially strong determinant of costs.

5.3 POLICY IMPLICATIONS

Health economic analyses are used to aid decision making in healthcare to ensure efficient use of healthcare resources. This is accomplished at several different levels, from understanding burden of a disease and where gains can be attained, to a specific assessment of a therapy and whether it should be paid for within the general reimbursement system/covered in health plans or not. In Sweden, economic evaluations have been used to a large extent in decision making about healthcare policies and in treatment decisions (101).

This thesis has shown that quality register data can be used in a wide range of health economic analyses, providing increased knowledge about the health economic consequences of diseases and therapies. In combination with other data sources, this is an important base for making informed policy decisions and to understand also on hospital level where cost-effective improvements of healthcare delivery may be attained.

In economic evaluations of therapies at market introduction, the use of RCT data may provide a good prediction of real life cost-effectiveness on which reimbursement decisions are made. In an RCT based analysis, the comparator is often placebo which is not a real

treatment alternative in clinical practice. One may argue that this is not a relevant comparator for a decision on resource allocation as the results indicate whether resources should be spent on the therapy or placebo (which is not offered in clinical practice). On the other hand, it may be argued that the effect society should pay for is the placebo-controlled effect and therefore is the relevant comparison for basis of the decision of resource allocation. In any case, caution needs to be taken of the assumptions made in relation to the data and sensitivity analyses should be performed to better mirror the projected use in clinical practice in addition to the RCT-based analyses, to give a range of the results as a basis for the decision on resource allocation. As the therapies evaluated become standard therapies, as experiences from them changes the use or as new therapies enter the market, it is of importance to perform follow-up health economic evaluations to ensure a continuous cost-effective use in clinical practice.

The introduction of biological DMARDs have revolutionized RA-care by offering effective treatment and prolonging time to progression for the patients (14). These treatments have been recommended as treatment for RA in Sweden (11), which comes with an additional cost. The results from papers I and II indicated that whether or not these therapies are used in a cost-effective manner will be determined by the patient's age at treatment initiation and the rate of progression for the patient in the absence of biological treatment. Patient selection based on age may not be warranted as it would impose inequalities and discrimination in healthcare, which is not desirable. However, the patient's disease projections without biological treatment should be taken into consideration if healthcare spending are to be used cost-effectively. Policies and recommendations on cost-effective use of these treatments could be further refined for specific sub-groups of the patient population as more sub-groups analyses of cost-effectiveness are presented. Still, other important principals for decisions on resource allocation should also be considered, such as equality, severity of disease, patient need and other ethical aspects.

To improve health equity and increase value of healthcare, it is important to first identify possible inequalities in healthcare that considers both health outcomes and resources. Sweden has favourable conditions for such an analysis due to the quality and availability of national registers, both quality registers and other national registers. Based on such data, the results of paper IV has demonstrated statistically significant variations in health outcomes, not explained by the detected differences in patient mix. Thus, this indicated inequalities on hospital level in Swedish stroke care delivery, during both the acute phase and beyond. These results could help foster the sharing of best practices between hospitals and between regions, changing health policy and healthcare delivery at hospitals and within regions. This effect can be further enhanced when comparisons are performed and transparently communicated on a continuous basis. Healthcare organization of regions and other structural features, could potentially explain parts of the differences identified in paper IV. These factors are possible to control on hospital or regional level, whereby improvements are possible which would most likely be cost-effective. Potentially both an increase in health outcomes for patients with stroke in Sweden and more efficient use of resources could be achieved. Additionally, there is

most likely a possibility to decrease inequalities between patients treated at different hospitals and in different regions.

The results from paper V emphasize the importance of fast and efficient management of stroke patients to decrease the likelihood of permanent functional disability and the cost-consequences associated with this attained disability. Also, interventions such as reperfusion therapy (thrombolysis and thrombectomy) that can dramatically improve outcome for IS can be cost-effective even if the initial cost may be high, due to the long-term costs associated with worse functional disability. The results of this paper also highlighted the importance of including all costs irrespective of who incurs them in such analyses, and not only assess the impact on separate budgets (e.g. clinical budget at a hospital) as this may lead to sub-optimal policy decisions for society at large. The need of continuous rehabilitation to maintain functional ability is also of importance, not only for the individual patient by reaching better health outcomes, but also for society at large, in decreasing the societal burden of stroke by keeping patients in better health states associated with lower costs. Due to the chronic nature of these disabilities, the long-term cost consequences are likely to be substantial. These results may hence be used as basis for policy decisions of management of stroke patients, by providing information on the cost-offset of keeping patients in levels of better functional ability. This may be useful both with regards to acute therapy and rehabilitation efforts. The results may further be used as input data in economic evaluations of interventions in stroke care.

5.4 SUGGESTIONS FOR FUTURE RESEARCH

Although quality registers are not designed for health economic purposes, they provide a unique opportunity to assess different diseases from a health economic point of view to help make efficient use of healthcare resources. This opportunity should be further explored in future research and more assessments should take advantage of linking data to other registers for holistic approaches in health economic analyses of diseases.

The market entry of anti-TNFs provided an important treatment alternative and a potential for health improvement for patients with RA, halting disease progression and prolonging the time to functional disability. However, these therapies have been costly and have put a constraint on healthcare budgets whereby the health economic analyses of these therapies have been important to ensure cost-effective use. Future research should continue to assess different sub-populations, new treatment regimens or dosing schemes (for example with treatment holidays) to ensure as cost-effective use as possible while maintaining the positive health effects of these therapies. To date, there is scarce evidence of difference in effects between different biological DMARDs (102) and head-to-head trials are needed to assess this. When such data becomes available, it is important to perform follow-up cost-effectiveness assessments as basis for policy decisions of the comparative cost-effectiveness of different options of biological DMARDs.

In stroke, thrombolysis and thrombectomies have had a similar effect on patient outcomes for stroke patients as biological DMARDs have had for RA, as they have been shown to decrease the risk of long-term functional disability of stroke. These therapies are associated with an increased cost, but recent publications based on clinical trial data suggest that their use are cost-effective (78, 103-106). Quality registers for stroke should be used to continuously monitor the effectiveness of these new acute therapies and to provide data for cost-effectiveness assessments of these therapies in clinical practice. This is important to ensure that the treatments are used in a cost-effective manner in clinical practice. As thrombectomy is not available yet at all hospitals in Sweden it should be possible to match patients for an economic evaluation of its use in clinical practice, as a complement to evaluations performed based on RCT data (106). In such assessments, it is of importance to model the long-term effect of this chronic condition and not only for the year the patients are monitored within the quality register. The results in paper V can be used for populating the model with costs based on functional disability and stroke type during the first and second year, thereafter assumptions need to be made to the long-term effects. As stroke is not a progressive disease, rather the condition reached after one year is expected to be relatively static in absence of new events, the costs of the second year related to the stroke could be assumed to prevail during following years as well. The vast experience of evaluating treatments for RA to model life-time consequences, such as choice of comparator and sensitivity analyses related to this, as well as necessary assumptions of long-term effectiveness, should be applied in any model for an evaluation of stroke therapy.

Additionally, updated costs and utility assessments of RA related to health outcomes are warranted as these may have changed over time in a Swedish setting. In stroke, utility assessments and its relation to functional disability and resource use/costs would also be of great interest. Such studies would provide deeper insights into the health economic consequences of stroke and RA to date, and also provide updated data for use in economic evaluations, increasing the validity and predictability of such analyses.

5.5 LEARNINGS AND CONCLUSIONS

This thesis has demonstrated the strengths and limitations of using data from quality registers for health economic analyses in patients with chronic conditions. This thesis has used the data for several purposes, building on the learnings from each paper included in this thesis:

- Paper I included one quality register data source, complemented with published data. An assessment was made on one therapy in a health economic model, modelling long-term effects in a chronic disease. Challenges in using register data for real life cost-effectiveness assessments were addressed.
- Paper II included three similar quality register sources, including several treatment options and lines of biological therapy. To enable this analyses, modifications to the health economic model was necessary and more extensive sensitivity analyses were performed, increasing the understanding of drivers of the results.

- Paper III included two different data sources (quality register and RCT) and thereby two different patient populations, in order to assess the impact of different sources and their characteristics as well as the impact of assumptions made in the model on the results. For this paper, a matched cohort from the register was elicited to enable comparison to the RCT cohort to ensure that similar populations were used in the evaluation.
- Paper IV expanded the number of data sources, enabling a larger number of variables to be included, which required work with data linkage as well as assessing differences in data quality and registration between the PAS of different regions. Identification and estimation of both health outcomes and resource use from the compiled register dataset was practiced. Instead of comparing outcomes between two treatment alternatives, this paper compared outcomes and resources between different hospitals and regions. Rather than matching populations for the different hospitals, the analyses were adjusted for differences in patient mix by the use of statistical analysis.
- Paper V transformed the resources into costs, using the costing aspect of health economics. This was done by functional disability and stroke type, enabling the use of these results in future health economic evaluations of therapies in stroke care. Stratified analysis was also performed by age.

The quality registers are not designed for health economic purposes, but this thesis has demonstrated their valuable contribution in health economics by providing a valid base of data and opportunities to:

- Assess real life effectiveness of treatments in economic evaluations
- Retrieve data on health outcomes and patient characteristics, which are essential in:
 - Measuring health outcomes and relating them to levels of resource use
 - Enabling hospital comparisons of performance and performing case-mix adjustment of results
 - Enabling stratification of cost estimates by level of health outcome
 - Provide input parameters for future economic evaluations

In order to assess the full health economic aspects of chronic conditions, quality registers play an important role, but there is a necessity to combine the quality register data with other registers or other data sources, published literature and potentially also conduct modelling to account for the long-term effects. Nevertheless, any quality register that wants to ensure that the data can be used for health economic analyses and provide valid data for such analyses, should consider to:

- Ensure long-term follow-up of the patients (especially in chronic conditions)
- Collect data on:
 - Patient characteristics, including the clinical markers important for the patient's prognosis
 - Treatments received

- Health outcomes that are common as measurements of treatment outcome (e.g. in RCTs), as well as estimation of quality of life or utilities
- Resource use (quantifiable) outside the healthcare sector, e.g. informal care

The quality registers and other register data sources can be utilized to a greater extent in different assessments which share the aim of improving healthcare delivery and increasing its value – either by assessing level of health outcomes, processes and resources used; enabling comparisons between treatments or hospitals; or assessing determinants for different outcomes.

6 ACKNOWLEDGEMENTS

A special thanks to a number of people and institutions who have supported me in various ways throughout my PhD-studies:

Fredrik Borgström, my main supervisor, for leading me through a unique form of mushroom management. Nevertheless, always providing substantial feedback, interesting discussions and sarcastic comments. Thank you for introducing me to health economics and making me a health economist!

Hélène Pessah-Rasmussen, my co-supervisor and the one responsible for getting my act together and finally finishing off my PhD-studies. Thank you for sharing your vast expertise in Swedish stroke care and management of stroke patients.

Ronald van Vollenhoven, my co-supervisor, for sharing your expertise in RA and the evolvement of RA treatments.

Gisela Kobelt, my co-supervisor in the beginning of my PhD-studies, for sharing your deep understanding in RA and its consequences for patients as well as all health economic aspects of RA.

Ragnhild Mogren, my external mentor, beloved cousin and friend. I made it! You're up next.

Former Stockholm Health Economics (including all the name changes thereafter) and Ivbar Institute for enabling my PhD-studies. Thanks to Schering Plough AB, MSD, Pfizer, Sveus and Forte for financial support of the specific papers. I appreciate this opportunity for higher education, improvement of knowledge, personal development and increasing scientific qualifications. Without this support this thesis would not have been possible.

All co-authors, especially **Carl Willers**, for substantial feedback and good teamwork, making the publications better and the work with the studies more enjoyable!

Dear colleagues at both former Stockholm Health Economics and Ivbar Institute, for interesting discussions and fun times! A special thanks to those of you who also have become my confidants at work and friends outside of the office – you make my working life easier and more rewarding!

Dear friends (both old and new) who always support me and fulfil my life with insightful discussion, joy and laughter! My old friends in the Falun-crew, my PolMag-friends (I know what you all think, “the PhD is in the wrong subject”) and friends from my fun times at V-Dala. The Mörsa-people including continuously expanding number of kids - let us always have the Mörsa-trips! And, of course, all other friends that I have the pleasure to have in my life.

My parents: **Thomas** and **Gudrun**. Allowing me to take my own paths in life and supporting me in my choices. Still I ended up as a health economist, a sweet mixture of your respective professional identities! Thanks to you and my in-laws **Karin** and **Uno**, for making my everyday life easier and always helping us out with the kids! You are all wonderful grandparents.

My supportive brothers **Magnus** and **Göran** with families. You all bring happiness to my life (and a bit of agony) and I know that you're always there for me and my family.

Daniel, Siri and **Frank**, thanks for being the most important people in my life and for making me complete.

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